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(54) **SUBSTITUTED PYRROLO[2,3-B]PYRAZINES AS FGFR INHIBITORS**

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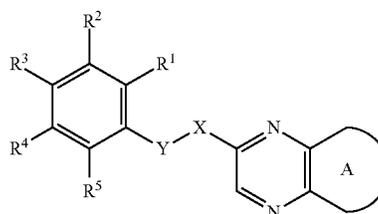
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(57)

ABSTRACT

The present invention relates to pyrazine derivatives of Formula I, and pharmaceutical compositions including the same, that are inhibitors of one or more FGFR enzymes and are useful in the treatment of FGFR-associated diseases such as cancer.



21 Claims, No Drawings

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**SUBSTITUTED PYRROLO[2,3-B]PYRAZINES
AS FGFR INHIBITORS**

FIELD OF THE INVENTION

The present invention relates to pyrazine derivatives, and pharmaceutical compositions including the same, that are inhibitors of one or more FGFR enzymes and are useful in the treatment of FGFR-associated diseases such as cancer.

BACKGROUND OF THE INVENTION

The Fibroblast Growth Factor Receptors (FGFR) are receptor tyrosine kinases that bind to fibroblast growth factor (FGF) ligands. There are four FGFR proteins (FGFR1-4) that are capable of binding ligands and are involved in the regulation of many physiological processes including tissue development, angiogenesis, wound healing, and metabolic regulation. Upon ligand binding, the receptors undergo dimerization and phosphorylation leading to stimulation of the protein kinase activity and recruitment of many intracellular docking proteins. These interactions facilitate the activation of an array of intracellular signaling pathways including Ras-MAPK, AKT-PI3K, and phospholipase C that are important for cellular growth, proliferation and survival (Reviewed in Eswarakumar et al. Cytokine & Growth Factor Reviews, 2005).

Aberrant activation of this pathway either through overexpression of FGF ligands or FGFR or activating mutations in the FGFRs can lead to tumor development, progression, and resistance to conventional cancer therapies. In human cancer, genetic alterations including gene amplification, chromosomal translocations and somatic mutations that lead to ligand-independent receptor activation have been described. Large scale DNA sequencing of thousands of tumor samples has revealed that components of the FGFR pathway are among the most frequently mutated in human cancer. Many of these activating mutations are identical to germline mutations that lead to skeletal dysplasia syndromes. Mechanisms that lead to aberrant ligand-dependent signaling in human disease include overexpression of FGFs and changes in FGFR splicing that lead to receptors with more promiscuous ligand binding abilities (Reviewed in Knights and Cook Pharmacology & Therapeutics, 2010; Turner and Grose, Nature Reviews Cancer, 2010). Therefore, development of inhibitors targeting FGFR may be useful in the clinical treatment of diseases that have elevated FGF or FGFR activity.

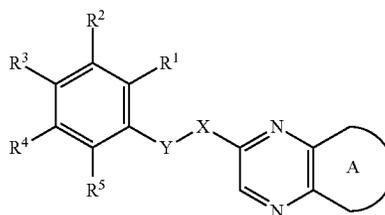
The cancer types in which FGF/FGFRs are implicated include, but are not limited to: carcinomas (e.g., bladder, breast, cervical, colorectal, endometrial, gastric, head and neck, kidney, liver, lung, ovarian, prostate); hematopoietic malignancies (e.g., multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myelogenous leukemia, non-Hodgkin lymphoma, myeloproliferative neoplasms, and Waldenstrom's Macroglobulinemia); and other neoplasms (e.g., glioblastoma, melanoma, and rhabdomyosarcoma). In addition to a role in oncogenic neoplasms, FGFR activation has also been implicated in skeletal and chondrocyte disorders including, but not limited to, achondroplasia and craniosynostosis syndromes.

There is a continuing need for the development of new drugs for the treatment of cancer and other diseases, and the FGFR inhibitors described herein help address this need.

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SUMMARY OF THE INVENTION

The present invention provides, inter alia, a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

The present invention further provides a composition comprising a compound of Formula I and at least one pharmaceutically acceptable carrier.

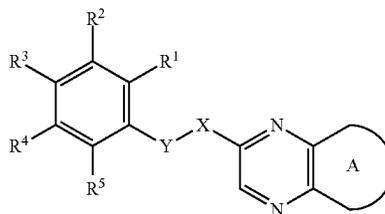
The present invention further provides a method of treating cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of treating a myeloproliferative disorder in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides a skeletal or chondrocyte disorder in a patient comprising administering to the patient a therapeutically effective amount of Formula I, or a pharmaceutically acceptable salt thereof.

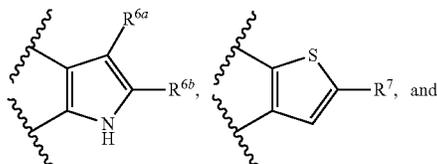
DETAILED DESCRIPTION

The present invention is related to FGFR inhibitors such as a compound of Formula I:

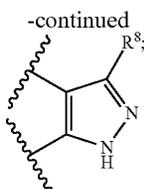


or a pharmaceutically acceptable salt thereof, wherein:
X and Y are each independently selected from CH₂, O, and S; wherein no more than one of X and Y is selected from O and S;

ring A is selected from



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R¹, R², R³, R⁴, and R⁵ are each independently selected from H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, CN, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^eR^f, NR^eC(O)R^b, NR^eC(O)OR^a, NR^eC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^eC(=NR^e)NR^cR^d, NR^eS(O)R^b, NR^eS(O)R^cR^d, NR^eS(O)₂R^b, NR^eS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ haloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^eC(=NR^e)NR^cR^d, NR^eR^f, NR^eC(O)R^b, NR^eC(O)OR^a, NR^eC(O)NR^cR^d, NR^eS(O)R^b, NR^eS(O)₂R^b, NR^eS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R^e is selected from H, C₁₋₄ alkyl, CN, and C₁₋₄ alkoxy;

R^{6a}, R^{6b}, R⁷ and R⁸ are each independently selected from H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{e1}R^{f1}, NR^{e1}C(O)R^{b1}, NR^{e1}C(O)OR^{a1}, NR^{e1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{e1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{e1}S(O)R^{b1}, NR^{e1}S(O)₂R^{b1}, NR^{e1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R⁹;

each R⁹ is independently selected from Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{e1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{e1}R^{f1}, NR^{e1}C(O)R^{b1}, NR^{e1}C(O)OR^{a1}, NR^{e1}C(O)NR^{c1}R^{d1}, NR^{e1}S(O)R^{b1}, NR^{e1}S(O)₂R^{b1}, NR^{e1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{e1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{e1}R^{f1}, NR^{e1}C(O)R^{b1}, NR^{e1}C(O)OR^{a1}, NR^{e1}C(O)NR^{c1}R^{d1}, NR^{e1}S(O)R^{b1}, NR^{e1}S(O)₂R^{b1}, NR^{e1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, NR^{e2}R^{f2}, NR^{e2}C(O)R^{b2}, NR^{e2}C(O)OR^{a2}, NR^{e2}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{e2}C(=NR^{e2})NR^{c2}R^{d2};

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NR^{e2}R^{f2}, NR^{e2}S(O)R^{b2}, NR^{e2}S(O)₂R^{b2}, NR^{e2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{e2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{e2}R^{f2}, NR^{e2}C(O)R^{b2}, NR^{e2}C(O)OR^{a2}, NR^{e2}C(O)NR^{c2}R^{d2}, NR^{e2}S(O)R^{b2}, NR^{e2}S(O)₂R^{b2}, NR^{e2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, (5-10 membered heteroaryl)-C₁₋₄ alkyl, or (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, (5-10 membered heteroaryl)-C₁₋₄ alkyl, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, NR^{e3}S(O)R^{b3}, NR^{e3}S(O)₂R^{b3}, NR^{e3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, NR^{e3}S(O)R^{b3}, NR^{e3}S(O)₂R^{b3}, NR^{e3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}; wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, NR^{e3}S(O)R^{b3}, NR^{e3}S(O)₂R^{b3}, NR^{e3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, NR^{e3}S(O)R^{b3}, NR^{e3}S(O)₂R^{b3}, NR^{e3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}; wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{e3}R^{f3}, NR^{e3}C(O)R^{b3}, NR^{e3}C(O)OR^{a3}, NR^{e3}C(O)NR^{c3}R^{d3}, NR^{e3}S(O)R^{b3}, NR^{e3}S(O)₂R^{b3}, NR^{e3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

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$\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{C}(\text{=NR}^{\text{e}3})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{=NR}^{\text{e}3})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$;

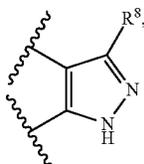
each $\text{R}^{\text{e}1}$ and $\text{R}^{\text{e}2}$ is independently selected from H, C_{1-4} alkyl, CN, $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{b}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, and $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$;

each $\text{R}^{\text{a}3}$, $\text{R}^{\text{b}3}$, $\text{R}^{\text{c}3}$, and $\text{R}^{\text{d}3}$ is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any $\text{R}^{\text{c}3}$ and $\text{R}^{\text{d}3}$ together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy; and

each $\text{R}^{\text{e}3}$ is independently selected from H, C_{1-4} alkyl, and CN;

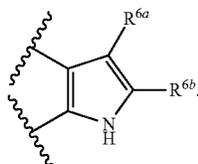
wherein when ring A is



R^8 is H, and X is O, then at least one of R^1 , R^2 , R^3 , R^4 , and R^5 is other than H.

In some embodiments, X and Y are both CH_2 .

In some embodiments, ring A is



In some embodiments, R^{6a} is H, halo, C_{1-6} alkyl, CN, or $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$.

In some embodiments, R^{6a} is H, Br, Cl, methyl, ethyl, CN, or $\text{C}(\text{O})\text{NHCH}_3$.

In some embodiments, R^{6a} is H.

In some embodiments, R^{6b} is other than H.

In some embodiments, R^{6b} is C_{1-6} alkyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, or $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$; wherein said C_{1-6} alkyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9 .

In some embodiments, R^{6b} is phenyl, thienyl, pyrazolyl, pyridyl, pyrimidinyl, benzodioxolyl, 1,2,3,6-tetrahydropyridinyl, 1H-indazolyl, piperidinyl, pyridopyrazinyl, indolinonyl; wherein said phenyl, thienyl, pyrazolyl, pyridyl, pyrimidinyl, benzodioxolyl, 1,2,3,6-tetrahydropyridinyl, 1H-indazolyl, piperidinyl, pyridopyrazinyl, indolinonyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9 .

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In some embodiments, R^{6b} is propyl or propynyl; wherein said propyl or propynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9 .

In some embodiments, R^{6b} is $\text{C}(\text{O})\text{NHCH}_3$ or $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$.

In some embodiments, R^{6b} is propyl, propynyl, phenyl, thienyl, pyrazolyl, pyridyl, pyrimidinyl, a benzo[d][1,3]dioxole ring, 1,2,3,6-tetrahydropyridinyl, 1H-indazolyl, piperidinyl, pyrido[2,3-b]pyrazinyl, an indolin-2-one ring, $\text{C}(\text{O})\text{NHCH}_3$, or $\text{C}(\text{O})\text{N}(\text{CH}_3)_2$; wherein said propyl, propynyl, phenyl, thienyl, pyrazolyl, pyridyl, pyrimidinyl, benzo[d][1,3]dioxole ring, 1,2,3,6-tetrahydropyridinyl, 1H-indazolyl, piperidinyl, pyrido[2,3-b]pyrazinyl, and indolin-2-one ring are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9 .

In some embodiments, R^9 is Cy^1 , halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, $\text{OR}^{\text{a}1}$, $\text{SR}^{\text{b}1}$, $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, or $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{R}^{\text{b}1}$, wherein said C_{1-6} alkyl, is optionally substituted with 1, 2, or 3 substituents independently selected from Cy^1 , halo, CN, NO_2 , $\text{OR}^{\text{a}1}$, $\text{SR}^{\text{b}1}$, $\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{OC}(\text{O})\text{R}^{\text{b}1}$, $\text{OC}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{C}(\text{=NR}^{\text{e}1})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{=NR}^{\text{e}1})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{OR}^{\text{a}1}$, $\text{NR}^{\text{c}1}\text{C}(\text{O})\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{R}^{\text{b}1}$, $\text{NR}^{\text{c}1}\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$, $\text{S}(\text{O})\text{R}^{\text{b}1}$, $\text{S}(\text{O})_2\text{R}^{\text{b}1}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}1}\text{R}^{\text{d}1}$.

In some embodiments Cy^1 is morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, tetrahydropyranyl, tetrahydropyridinyl, pyrrolidinonyl, piperazinonyl, or piperidinonyl, wherein said Cy^1 is optionally substituted with 1, 2, or 3 substituents independently selected from halo, C_{1-6} alkyl, and $\text{OR}^{\text{a}2}$.

In some embodiments, at least two of R^1 , R^2 , R^3 , R^4 , and R^5 are other than H.

In some embodiments, at least three of R^1 , R^2 , R^3 , R^4 , and R^5 are other than H.

In some embodiments, at least four of R^1 , R^2 , R^3 , R^4 , and R^5 are other than H.

In some embodiments, R^3 is H and R^2 and R^5 are other than H.

In some embodiments, R^3 is H and R^1 , R^2 , R^4 , and R^5 are other than H.

In some embodiments, R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from H, halo, and C_{1-4} alkoxy.

In some embodiments, R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from H, halo, and OR^{a} .

In some embodiments, R^3 is H and R^1 , R^2 , R^4 , and R^5 are each independently selected from halo and OR^{a} .

In some embodiments, R^3 is H and R^1 , R^2 , R^4 , and R^5 are each independently selected from halo and C_{1-4} alkoxy.

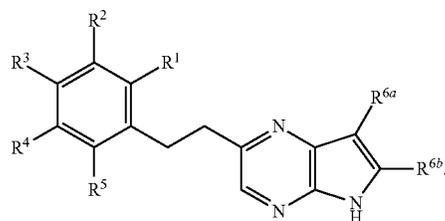
In some embodiments, R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from H, F, and methoxy.

In some embodiments, R^1 is H or F, R^2 is methoxy, R^3 is H, R^4 is methoxy, and R^5 is H or F.

In some embodiments, R^1 is H, R^2 is methoxy, R^3 is H, R^4 is methoxy, and R^5 is H.

In some embodiments, R^1 is F, R^2 is methoxy, R^3 is H, R^4 is methoxy, and R^5 is F.

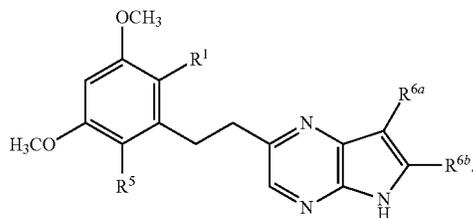
In some embodiments, the compounds of the invention have Formula IIa:



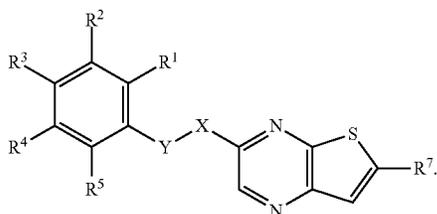
IIa

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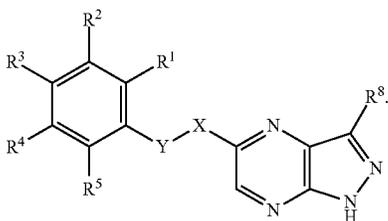
In some embodiments, the compounds of the invention have Formula IIb:



In some embodiments, the compounds of the invention have Formula III:



In some embodiments, the compounds of the invention have Formula IV:



It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C₁₋₆ alkyl" is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl.

At various places in the present specification various aryl, heteroaryl, cycloalkyl, and heterocycloalkyl rings are described. Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term "pyridyl," "pyridinyl," or "a pyridine ring" may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety

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where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

For compounds of the invention in which a variable appears more than once, each variable can be a different moiety independently selected from the group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R.

As used herein, the phrase "optionally substituted" means unsubstituted or substituted.

As used herein, the term "substituted" means that a hydrogen atom is replaced by a non-hydrogen group. It is to be understood that substitution at a given atom is limited by valency.

As used herein, the term "C_{i-j}", where i and j are integers, employed in combination with a chemical group, designates a range of the number of carbon atoms in the chemical group with i-j defining the range. For example, C₁₋₆ alkyl refers to an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms.

As used herein, the term "alkyl", employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched. In some embodiments, the alkyl group contains 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methyl-1-butyl, 3-pentyl, n-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group is methyl, ethyl, or propyl.

As used herein, "alkenyl", employed alone or in combination with other terms, refers to an alkyl group having one or more carbon-carbon double bonds. In some embodiments, the alkenyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, n-propenyl, isopropenyl, n-butenyl, sec-butenyl, and the like.

As used herein, "alkynyl", employed alone or in combination with other terms, refers to an alkyl group having one or more carbon-carbon triple bonds. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms.

As used herein, "halo" or "halogen", employed alone or in combination with other terms, includes fluoro, chloro, bromo, and iodo. In some embodiments, halo is F or Cl.

As used herein, the term "haloalkyl", employed alone or in combination with other terms, refers to an alkyl group having up to the full valency of halogen atom substituents, which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF₃, C₂F₅, CHF₂, CCl₃, CHCl₂, C₂Cl₅, and the like.

As used herein, the term "alkoxy", employed alone or in combination with other terms, refers to a group of formula —O-alkyl. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, "haloalkoxy", employed alone or in combination with other terms, refers to a group of formula —O-

(haloalkyl). In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms. An example haloalkoxy group is $-\text{OCF}_3$.

As used herein, “amino”, employed alone or in combination with other terms, refers to NH_2 .

As used herein, the term “alkylamino”, employed alone or in combination with other terms, refers to a group of formula $-\text{NH}(\text{alkyl})$. In some embodiments, the alkylamino group has 1 to 6 or 1 to 4 carbon atoms. Example alkylamino groups include methylamino, ethylamino, propylamino (e.g., n-propylamino and isopropylamino), and the like.

As used herein, the term “dialkylamino”, employed alone or in combination with other terms, refers to a group of formula $-\text{N}(\text{alkyl})_2$. Example dialkylamino groups include dimethylamino, diethylamino, dipropylamino (e.g., di(n-propyl)amino and di(isopropyl)amino), and the like. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “alkylthio”, employed alone or in combination with other terms, refers to a group of formula $-\text{S-alkyl}$. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term “cycloalkyl”, employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon including cyclized alkyl and alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3, or 4 fused, bridged, or spiro rings) ring systems. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings (e.g., aryl or heteroaryl rings) fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of cyclopentane, cyclohexene, cyclohexane, and the like, or pyrido derivatives of cyclopentane or cyclohexane. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo. Cycloalkyl groups also include cycloalkylidenes. The term “cycloalkyl” also includes bridgehead cycloalkyl groups (e.g., non-aromatic cyclic hydrocarbon moieties containing at least one bridgehead carbon, such as adamantan-1-yl) and spirocycloalkyl groups (e.g., non-aromatic hydrocarbon moieties containing at least two rings fused at a single carbon atom, such as spiro[2.5]octane and the like). In some embodiments, the cycloalkyl group has 3 to 10 ring members, or 3 to 7 ring members. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is a C_{3-7} monocyclic cycloalkyl group. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcamyl, tetrahydronaphthalenyl, octahydronaphthalenyl, indanyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, the term “cycloalkylalkyl”, employed alone or in combination with other terms, refers to a group of formula cycloalkyl-alkyl-. In some embodiments, the alkyl portion has 1 to 4, 1 to 3, 1 to 2, or 1 carbon atom(s). In some embodiments, the alkyl portion is methylene. In some embodiments, the cycloalkyl portion has 3 to 10 ring members or 3 to 7 ring members. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl portion is monocyclic. In some embodiments, the cycloalkyl portion is a C_{3-7} monocyclic cycloalkyl group.

As used herein, the term “heterocycloalkyl”, employed alone or in combination with other terms, refers to a non-aromatic ring or ring system, which may optionally contain

one or more alkenylene or alkynylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, sulfur, oxygen, and phosphorus. Heterocycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused, bridged, or spiro rings) ring systems. In some embodiments, the heterocycloalkyl group is a monocyclic or bicyclic group having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, sulfur and oxygen. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings (e.g., aryl or heteroaryl rings) fused (i.e., having a bond in common with) to the non-aromatic heterocycloalkyl ring, for example, 1,2,3,4-tetrahydro-quinoline and the like. Heterocycloalkyl groups can also include bridgehead heterocycloalkyl groups (e.g., a heterocycloalkyl moiety containing at least one bridgehead atom, such as azaadamantan-1-yl and the like) and spiroheterocycloalkyl groups (e.g., a heterocycloalkyl moiety containing at least two rings fused at a single atom, such as [1,4-dioxo-8-aza-spiro[4.5]decan-N-yl] and the like). In some embodiments, the heterocycloalkyl group has 3 to 10 ring-forming atoms, or about 3 to 8 ring forming atoms. In some embodiments, the heterocycloalkyl group has 2 to 20 carbon atoms, 2 to 15 carbon atoms, 2 to 10 carbon atoms, or about 2 to 8 carbon atoms. In some embodiments, the heterocycloalkyl group has 1 to 5 heteroatoms, 1 to 4 heteroatoms, 1 to 3 heteroatoms, or 1 to 2 heteroatoms. The carbon atoms or heteroatoms in the ring(s) of the heterocycloalkyl group can be oxidized to form a carbonyl, an N-oxide, or a sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, the heterocycloalkyl portion is a C_{2-7} monocyclic heterocycloalkyl group. In some embodiments, the heterocycloalkyl group is a morpholine ring, pyrrolidine ring, piperazine ring, piperidine ring, tetrahydropyran ring, tetrahydropyridine, azetidine ring, tetrahydrofuran ring, indoline ring, pyrrolidinone ring, piperazinone ring, piperidinone ring, or indolinone ring.

As used herein, the term “heterocycloalkylalkyl”, employed alone or in combination with other terms, refers to a group of formula heterocycloalkyl-alkyl-. In some embodiments, the alkyl portion has 1 to 4, 1 to 3, 1 to 2, or 1 carbon atom(s). In some embodiments, the alkyl portion is methylene. In some embodiments, the heterocycloalkyl portion has 3 to 10 ring members or 3 to 7 ring members. In some embodiments, the heterocycloalkyl group is monocyclic or bicyclic. In some embodiments, the heterocycloalkyl portion is monocyclic. In some embodiments, the heterocycloalkyl portion is a C_{2-7} monocyclic heterocycloalkyl group.

As used herein, the term “aryl”, employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2 fused rings) aromatic hydrocarbon moiety, such as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, and the like. In some embodiments, aryl groups have from 6 to 10 carbon atoms or 6 carbon atoms. In some embodiments, the aryl group is a monocyclic or bicyclic group. In some embodiments, the aryl group is phenyl or naphthyl.

As used herein, the term “arylalkyl”, employed alone or in combination with other terms, refers to a group of formula aryl-alkyl-. In some embodiments, the alkyl portion has 1 to 4, 1 to 3, 1 to 2, or 1 carbon atom(s). In some embodiments, the alkyl portion is methylene. In some embodiments, the aryl portion is phenyl. In some embodiments, the aryl group is a monocyclic or bicyclic group. In some embodiments, the arylalkyl group is benzyl.

As used herein, the term “heteroaryl”, employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2 or 3 fused rings) aromatic hydrocarbon

moiety, having one or more heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl group is a monocyclic or bicyclic group having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, sulfur and oxygen. Example heteroaryl groups include, but are not limited to, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrol, oxazolyl, benzofuryl, benzothieryl, benzthiazolyl, benzodioxolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, pyrrolyl, azolyl, quinolinyl, isoquinolinyl, benzisoxazolyl, imidazo[1,2-b]thiazolyl, pyridopyrazinyl, or the like. The carbon atoms or heteroatoms in the ring(s) of the heteroaryl group can be oxidized to form a carbonyl, an N-oxide, or a sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized, provided the aromatic nature of the ring is preserved. In some embodiments, the heteroaryl group has from 3 to 10 carbon atoms, from 3 to 8 carbon atoms, from 3 to 5 carbon atoms, from 1 to 5 carbon atoms, or from 5 to 10 carbon atoms. In some embodiments, the heteroaryl group contains 3 to 14, 4 to 12, 4 to 8, 9 to 10, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to 4, 1 to 3, or 1 to 2 heteroatoms.

As used herein, the term "heteroarylalkyl", employed alone or in combination with other terms, refers to a group of formula heteroaryl-alkyl-. In some embodiments, the alkyl portion has 1 to 4, 1 to 3, 1 to 2, or 1 carbon atom(s). In some embodiments, the alkyl portion is methylene. In some embodiments, the heteroaryl portion is a monocyclic or bicyclic group having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl portion has 5 to 10 carbon atoms.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of methylbenzyl-amine (e.g., S and R forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like. Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (e.g., dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the con-

comitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

The term, "compound," as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., in the form of hydrates and solvates) or can be isolated.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic acid salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Berge et al., *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

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Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The expressions, "ambient temperature," "room temperature," and "r.t.," as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20°C . to about 30°C .

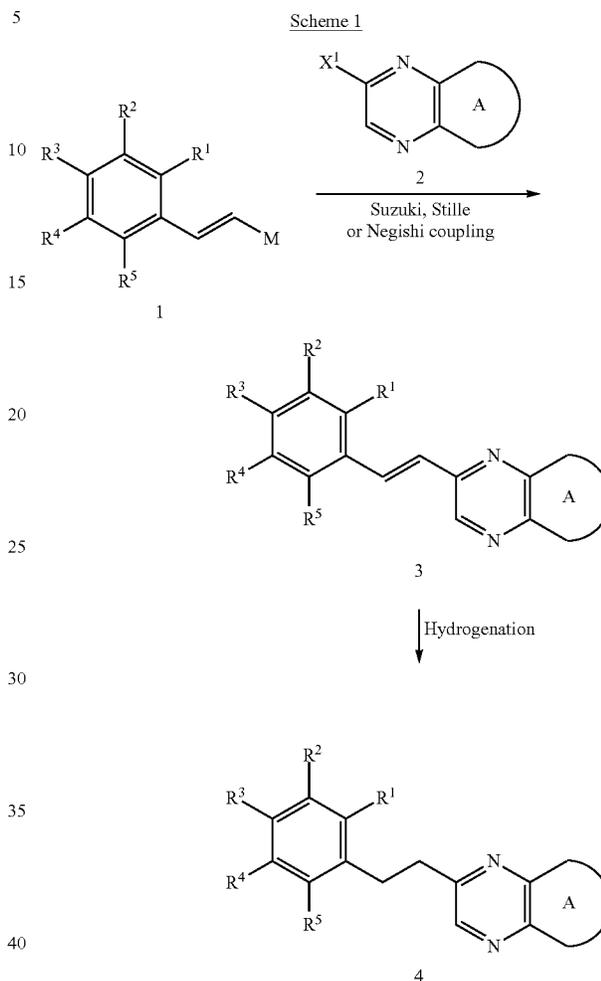
Compounds of the invention can be prepared according to numerous preparatory routes known in the literature. Example synthetic methods for preparing compounds of the invention are provided in the Schemes below.

The following abbreviations are used throughout: potassium acetate (KOAc), trimethylsilyl (TMS), N-methylpyrrolidone (NMP), lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS), sodium bis(trimethylsilyl)amide (NaHMDS), N-chlorosuccinimide (NCS), tetrahydrofuran (THF), 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), 1-hydroxy-7-azabenzotriazole (HOAT), 1,1'-carbonyldiimidazole (CDI), N-bromosuccinimide (NBS), N-iodosuccinimide (NIS), 2-trimethylsilylethoxymethyl chloride (SEMCl), and diethyl azodicarboxylate (DEAD).

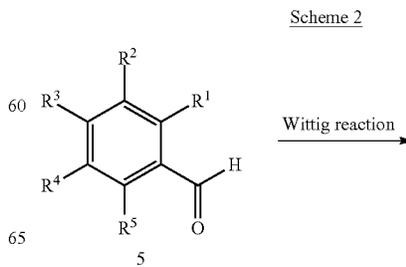
Compounds of formula 4 can be prepared by the methods outlined in Scheme 1. Halide 2 ($X^1 = \text{Cl}$, Br, or I) can be coupled to compound 1, where M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $\text{B}(\text{OH})_2$, $\text{Sn}(\text{Bu})_3$, or ZnBr), under standard Suzuki conditions or standard Stille conditions (e.g., in the presence of a palladium catalyst, such as, but not limited to, $\text{Pd}(\text{dppf})\text{Cl}_2$ and a phosphate or carbonate base) or standard Negishi conditions (e.g., in the presence of a palladium(0) catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)), to give compound 3. The following hydrogenation of compound 3

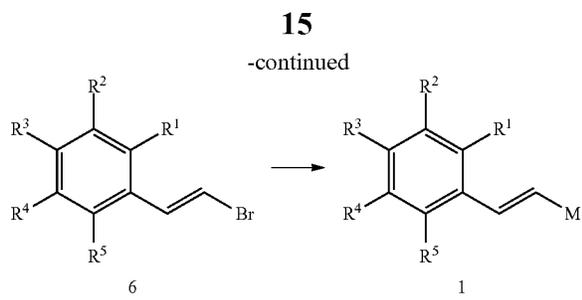
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using a suitable catalyst, such as, but not limited to, palladium (0) on carbon can afford formula 4.

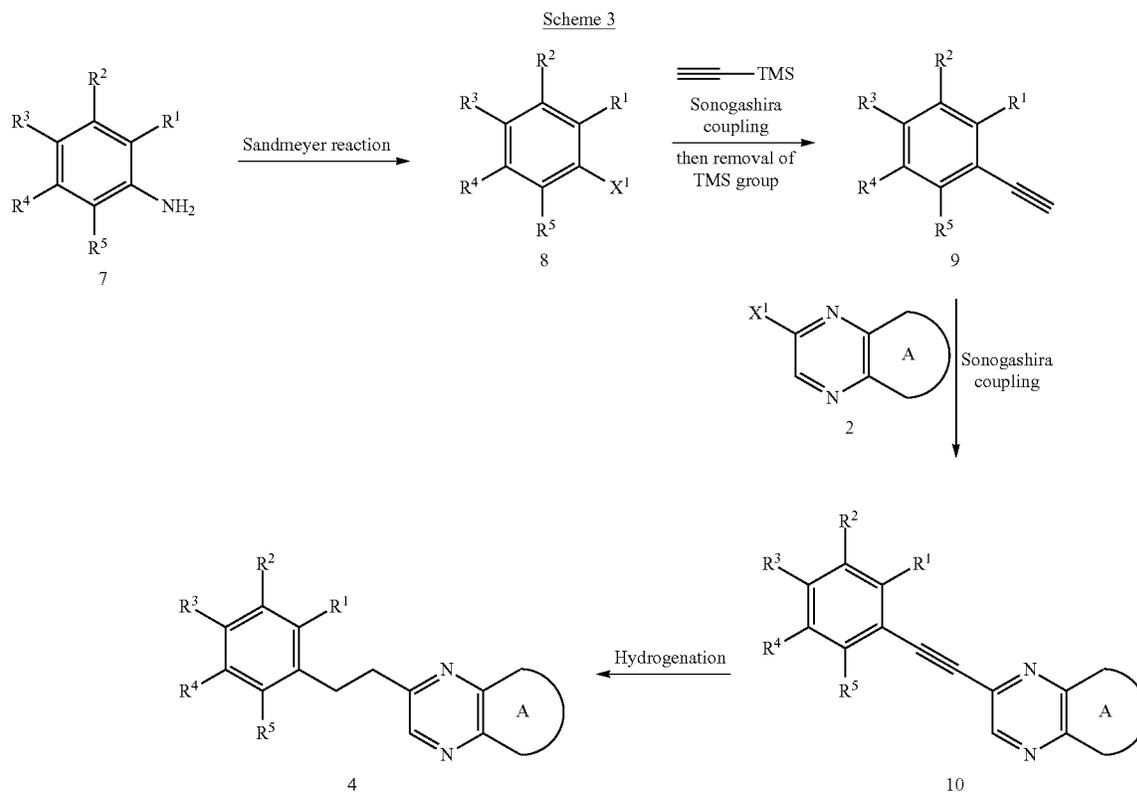


Compounds of formula 1 can be prepared by the methods outlined in Scheme 2. Vinyl bromide 6 can be prepared from aldehyde 5 using standard Wittig reaction conditions (e.g., in the presence of (bromomethyl)triphenylphosphonium bromide and a strong base such as, but not limited to, NaH, LiHMDS, KOtBu). Vinyl bromide 6 can be converted to the corresponding compound 1 under various conditions such as, but not limited to, bis(pinacolato)diboron/ $\text{Pd}(\text{dppf})\text{Cl}_2/\text{KOAc}$ for $\text{M} = \text{boronic ester}$, $n\text{BuLi}/\text{Bu}_3\text{SnCl}$ for $\text{M} = \text{Sn}(\text{Bu})_3$, and $n\text{BuLi}/\text{ZnBr}_2$ for $\text{M} = \text{ZnBr}$.

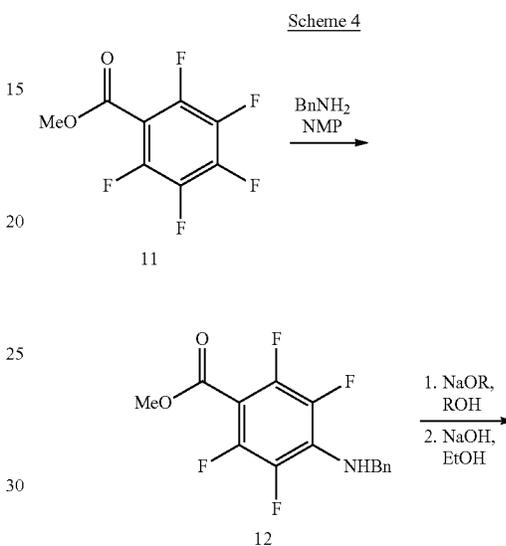




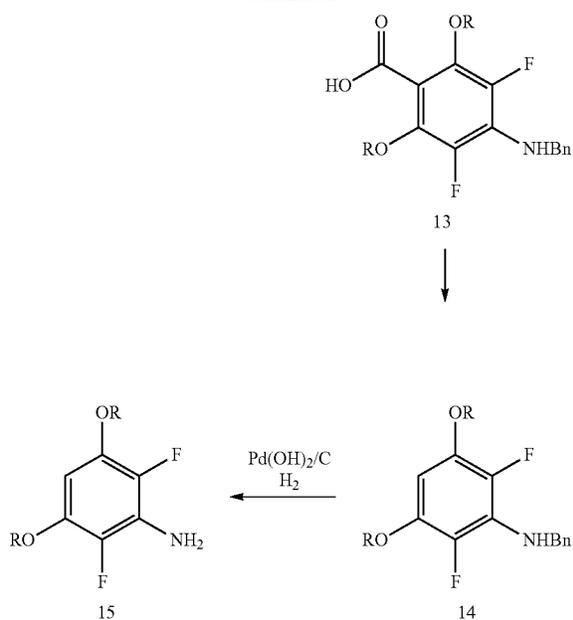
Alternatively, a series of compounds of formula 4 can be prepared by the methods outlined in Scheme 3. Appropriate aniline derivatives 7 can be converted to the corresponding halide 8 ($X^1 = \text{Cl}, \text{Br}, \text{or I}$) under standard Sandmeyer reaction conditions (e.g., aniline 7 reacts with sodium nitrite and hydrogen chloride to form an aryl diazonium salt, which decomposes in the presence of copper (I) bromide or potassium iodide to form the desired aryl halide). Halide 8 can be coupled with trimethylsilylacetylene under standard Sonogashira conditions (e.g., in the presence of a palladium(II) catalyst, such as, but not limited to, bis(triphenylphosphine)-palladium(II) dichloride, a Cu(I) salt, such as CuI or CuCN, and an amine, such as triethylamine). The removal of the trimethylsilyl group can generate compound 9. Compound 10 can be prepared by the coupling between compound 9 and halide 2 ($X^1 = \text{Cl}, \text{Br}, \text{or I}$) under the standard Sonogashira conditions (e.g., in the presence of a palladium(II) catalyst, such as, but not limited to, bis(triphenylphosphine)palladium (II) dichloride, a Cu(I) salt, such as CuI or CuCN, and an amine, such as triethylamine). Hydrogenation of compound 10 using a suitable catalyst, such as, but not limited to, palladium (0) on carbon can afford formula 4.

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A series of aniline derivatives 15 can be prepared according to the procedures described in Scheme 4 (see, e.g., WO 2011/093672). Displacement of fluorine in compound 11 with benzylamine provides the aniline 12 which can be converted to bis-ether by reacting with a suitable sodium alkoxide (NaOR where R is, e.g., methyl, alkyl). The following saponification can provide acid 13. Decarboxylation of benzoic acid 13, followed by hydrogenation using $\text{Pd}(\text{OH})_2/\text{C}$ can afford aniline 15.

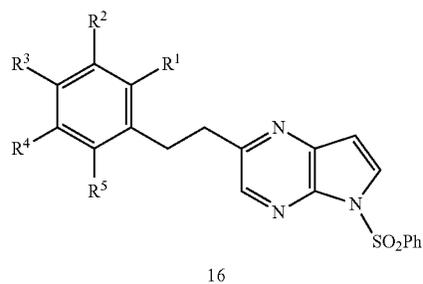


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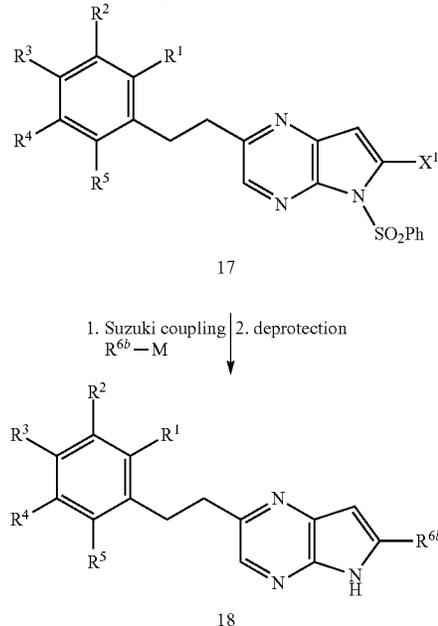
A series of 5H-pyrrolo[2,3-b]pyrazine derivatives 18 can be prepared according to the procedures outlined in Scheme 5. The halide 17 ($X^1 = \text{Cl}, \text{Br}, \text{or I}$) can be generated by the treatment of the compound 16, which is prepared using procedures as described in Scheme 1, with a strong base such as, but not limited to, LDA, LiHMDS, NaHMDS or butyllithium in an inert solvent such as THF, ether at low temperature to provide the metallated intermediate, and followed by the treatment with a halogen reagent such as, but not limited to, NCS, 1,2-dibromo-1,1,2,2-tetrachloroethane, or iodine. Halide 17 ($X^1 = \text{Cl}, \text{Br}, \text{or I}$) can be coupled to $R^{6b}\text{-M}$, where M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $\text{B}(\text{OH})_2$, $\text{Sn}(\text{Bu})_3$, or ZnBr), under standard Suzuki conditions or standard Stille conditions (e.g., in the presence of a palladium catalyst, such as, but not limited to, $\text{Pd}(\text{dppf})\text{Cl}_2$ and a phosphate or carbonate base) or standard Negishi conditions (e.g., in the presence of a palladium(0) catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)). Removal of the protecting group can afford compound 18.

Scheme 5



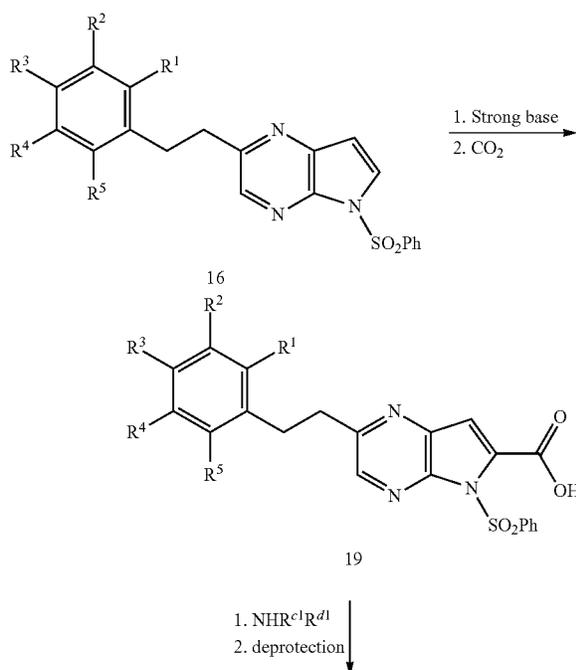
18

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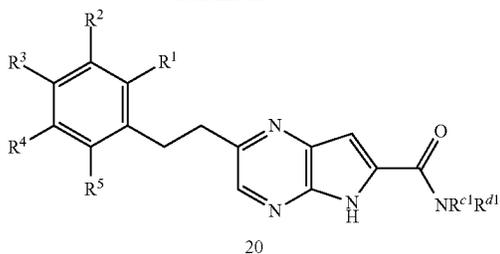
A series of amide derivatives 20 can be prepared according to the methods outlined in Scheme 6. The carboxylic acid 19 can be obtained by treating the compound 16 with a strong base such as, but not limited to, LDA, LiHMDS, NaHMDS, butyllithium in an inert solvent such as THF, ether at low temperature, and followed by addition of dry ice to the reaction mixture. Carboxylic acid 19 can be converted to the corresponding amide by coupling with an appropriate amine $\text{NHR}^{c1}\text{R}^{d1}$ in the presence of a suitable amide coupling reagent such as, but not limited to, HATU, HBTU, BOP, EDCI/HOBT, EDCI/HOAT, or CDI. Removal of the protecting group using a base such as, but not limited to, K_2CO_3 or KOtBu can provide amide 20.

Scheme 6



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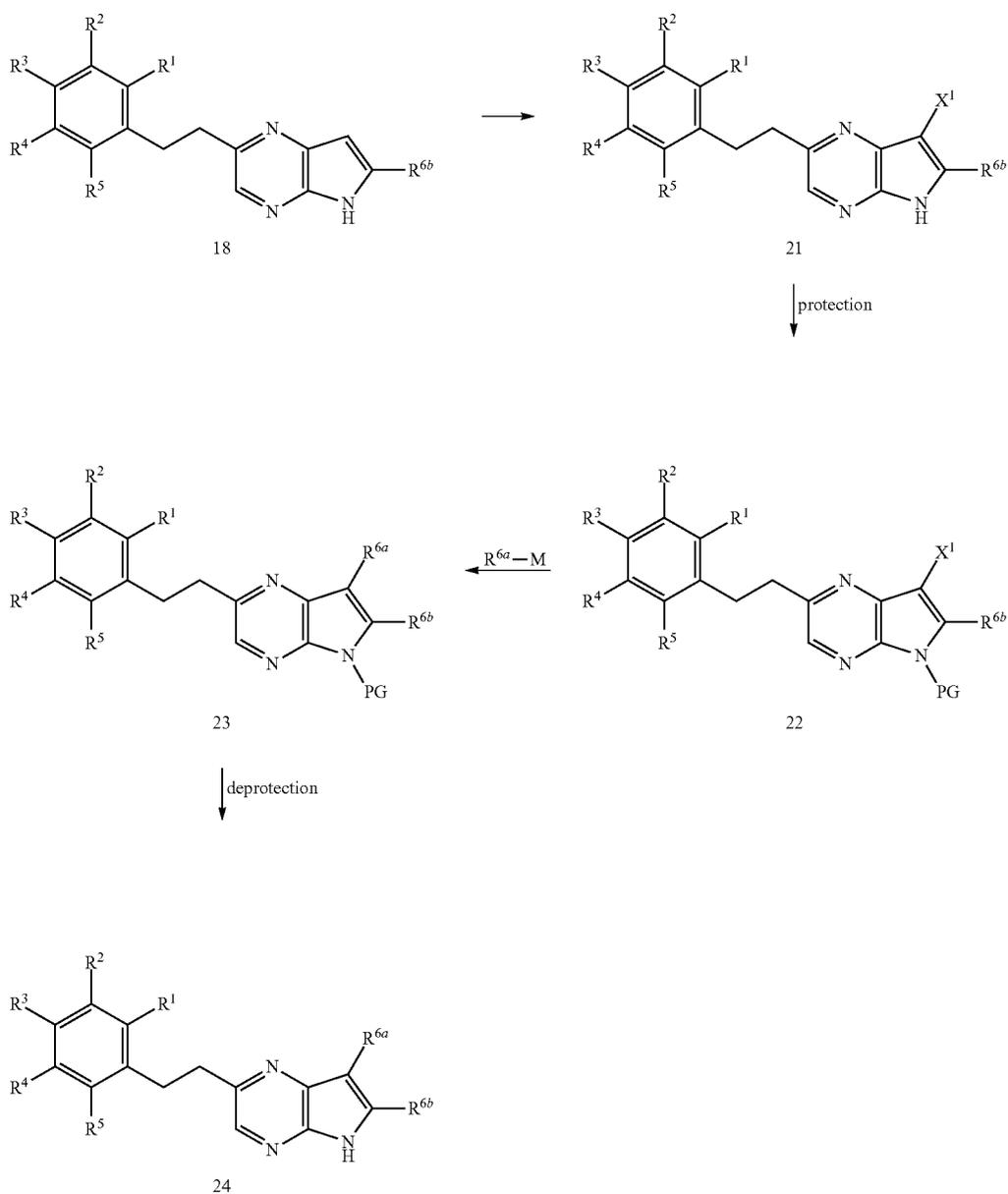


A series of 5H-pyrrolo[2,3-b]pyrazine derivatives 24 can be prepared according to the procedures outlined in Scheme

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7. Halogenation of compound 18 using a halogenating reagent such as, but not limited to, NCS, NBS or NIS can give the corresponding halide 21 ($X^1 = \text{Cl}, \text{Br}, \text{or I}$). Protection of halide 21 with suitable protection reagents such as, but not limited to, SEMCl under basic conditions can afford compound 22. Halide 22 ($X^1 = \text{Cl}, \text{Br}, \text{or I}$) can be coupled to $R^{6a}\text{-M}$, where M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $\text{B}(\text{OH})_2$, $\text{Sn}(\text{Bu})_3$, or ZnBr), under standard Suzuki conditions or standard Stille conditions (e.g., in the presence of a palladium catalyst, such as, but not limited to, $\text{Pd}(\text{dppf})\text{Cl}_2$ and a phosphate or carbonate base) or standard Negishi conditions (e.g., in the presence of a palladium(0) catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)), to give compound 23. Removal of the protecting group can afford compound 24.

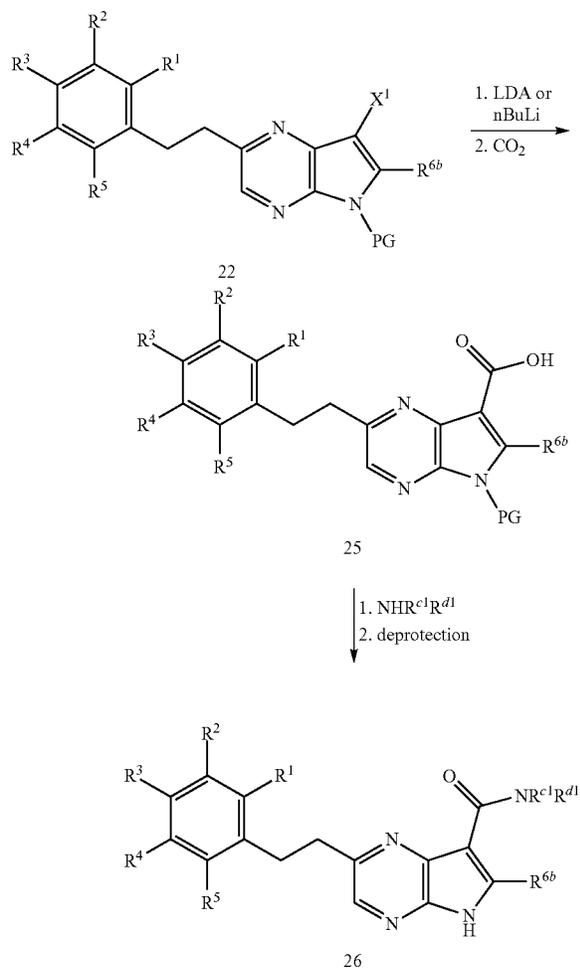
Scheme 7



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A series of 5H-pyrrolo[2,3-b]pyrazine derivatives 26 can be prepared according to the procedures outlined in Scheme 8. The carboxylic acid 25 can be obtained by treating the compound 22 with a strong base such as, but not limited to, LDA, or n-butyllithium in an inert solvent such as THF, ether at low temperature, and followed by addition of dry ice to the reaction mixture. Carboxylic acid 25 can be converted to the corresponding amide by coupling with an appropriate amine $\text{NHR}^{\text{c1}}\text{R}^{\text{d1}}$ in the presence of a suitable amide coupling reagent such as, but not limited to, HATU, HBTU, BOP, EDCI/HOBT, EDCI/HOAT, or CDI. Removal of the protecting group can provide compound 26.

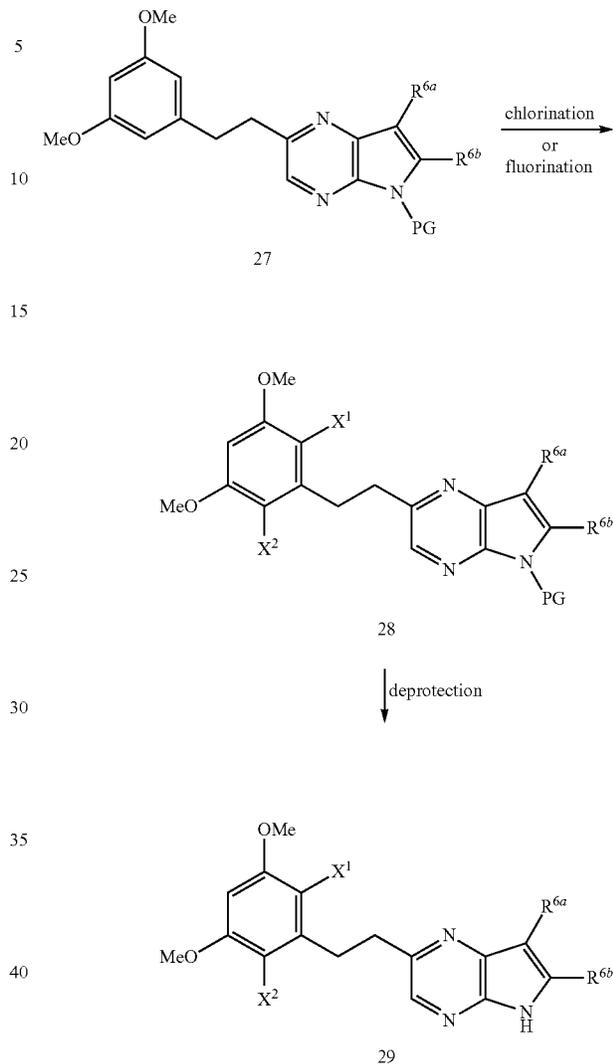
Scheme 8



A series of 5H-pyrrolo[2,3-b]pyrazine derivatives 29 can be prepared according to the procedures outlined in Scheme 9. Compound 27 can be prepared using procedures as described in the Scheme 7. Chlorination of compound 27 using appropriate reagents such as, but not limited to, sulfuryl chloride can give the corresponding monochloride ($\text{X}^1=\text{H}$, $\text{X}^2=\text{Cl}$) or dichloride ($\text{X}^1=\text{X}^2=\text{Cl}$). Alternatively, treating compound 27 with appropriate reagents such as, but not limited to, Selectfluor® can yield the corresponding monofluoride ($\text{X}^1=\text{H}$, $\text{X}^2=\text{F}$) or difluoride ($\text{X}^1=\text{X}^2=\text{F}$). The protecting group of compound 28 can be removed to give 5H-pyrrolo[2,3-b]pyrazine derivatives 29.

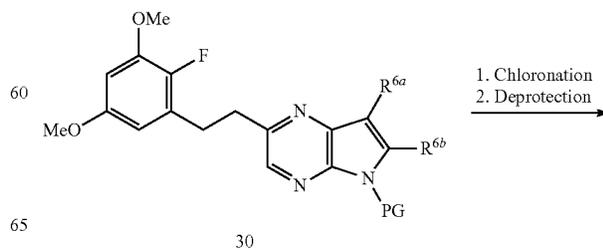
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Scheme 9

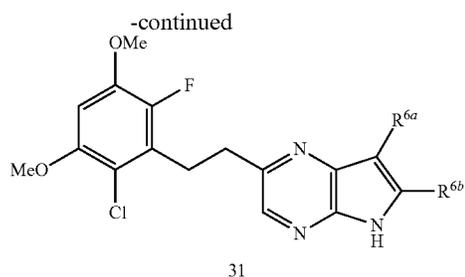


A series of 5H-pyrrolo[2,3-b]pyrazine derivatives 31 can be prepared according to the procedures outlined in Scheme 10. Monofluoride 30 can be prepared using procedures as described in the Scheme 9. Chlorination of compound 30 using appropriate reagents such as, but not limited to, sulfuryl chloride, followed by the deprotection can give 5H-pyrrolo[2,3-b]pyrazine derivatives 31.

Scheme 10

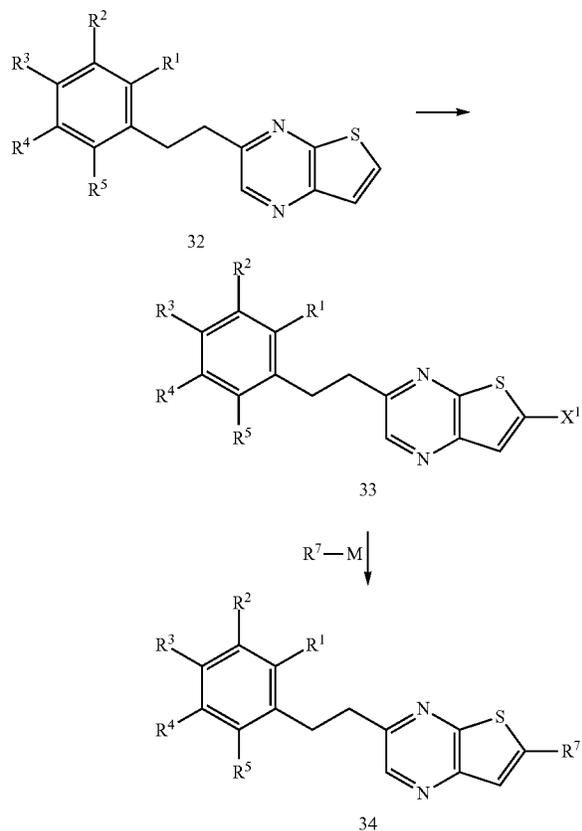


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A series of thieno[3,2-b]pyrazine derivatives 34 can be prepared according to the procedures outlined in Scheme 11. Compound 32 can be generated using procedures as described in the Scheme 3. Halogenation of compound 32 using a halogenating reagent such as, but not limited to, NCS, NBS, NIS can give halide 33 ($X^1=Cl, Br, \text{ or } I$). Halide 33 ($X^1=Cl, Br, \text{ or } I$) can be coupled to R^7-M , where M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $B(OH)_2$, $Sn(Bu)_3$, or $ZnBr$), under standard Suzuki conditions or standard Stille conditions (e.g., in the presence of a palladium catalyst, such as, but not limited to, $Pd(dppf)Cl_2$ and a phosphate or carbonate base) or standard Negishi conditions (e.g., in the presence of a palladium(0) catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)), to give compound 34.

Scheme 11

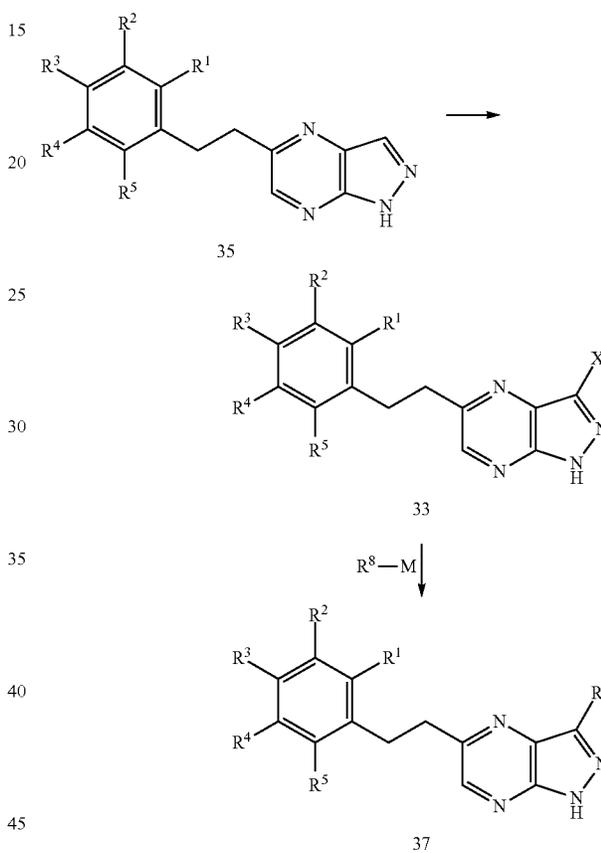


A series of 1H-pyrazolo[3,4-b]pyrazine derivatives 37 can be prepared according to the procedures outlined in Scheme 12. Compound 35 can be generated using procedures as described in the Scheme 3. Halogenation of compound 35

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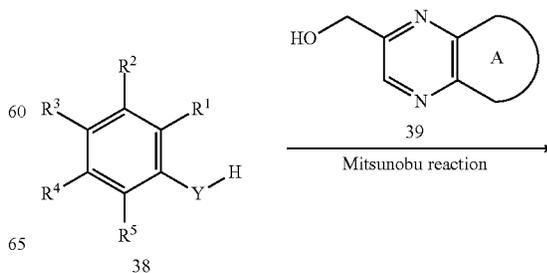
using a halogenating reagent such as NCS, NBS, or NIS can give halide 36 ($X^1=Cl, Br, \text{ or } I$). Halide 36 ($X^1=Cl, Br, \text{ or } I$) can be coupled to R^8-M , where M is a boronic acid, boronic ester or an appropriately substituted metal (e.g., M is $B(OH)_2$, $Sn(Bu)_3$, or $ZnBr$), under standard Suzuki conditions or standard Stille conditions (e.g., in the presence of a palladium catalyst, such as, but not limited to, $Pd(dppf)Cl_2$ and a phosphate or carbonate base) or standard Negishi conditions (e.g., in the presence of a palladium(0) catalyst, such as, but not limited to, tetrakis(triphenylphosphine)palladium(0)), to give compounds of formula 37.

Scheme 12

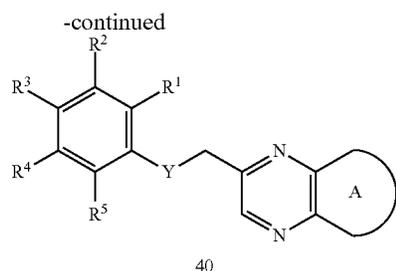


Compounds of formula 40 can be prepared according to the procedures outlined in Scheme 13. Compound 38 ($Y=O \text{ or } S$) can be coupled to alcohol 39 under standard Mitsunobu conditions (e.g., in the presence of PPh_3 and DEAD) to afford compound 40 ($Y=O \text{ or } S$).

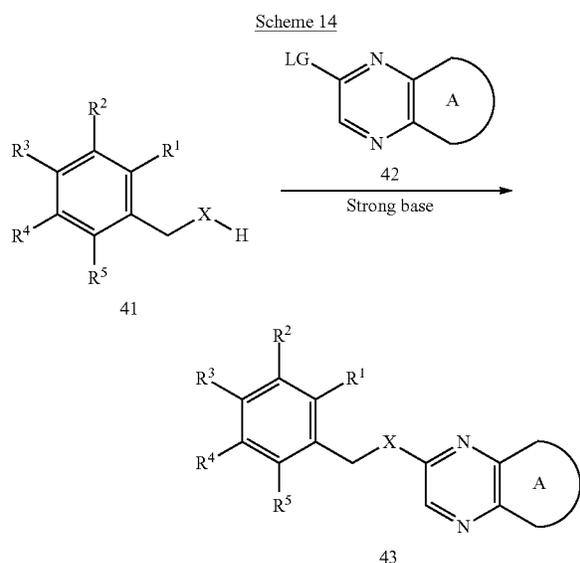
Scheme 13



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Compounds of formula 43 can be prepared according to the procedures outlined in Scheme 14. The treatment of compound 41 (X=O or S) with a strong base such as, but not limited to, NaH, LiHMDS, KOtBu, followed by the addition of compound 42 (LG=leaving group, such as, but not limited to, Cl, Br, or OMs) can afford compounds 43.



Methods of Use

Compounds of the invention can inhibit activity of one or more FGFR enzymes. For example, the compounds of the invention can be used to inhibit activity of an FGFR enzyme in a cell or in an individual or patient in need of inhibition of the enzyme by administering an inhibiting amount of a compound of the invention to the cell, individual, or patient.

In some embodiments, the compounds of the invention are inhibitors of one or more of FGFR1, FGFR2, FGFR3, and FGFR4. In some embodiments, the compounds of the invention inhibit each of FGFR1, FGFR2, and FGFR3. In some embodiments, the compounds of the invention are selective for one or more FGFR enzymes. In some embodiments, the compounds of the invention are selective for one or more FGFR enzymes over VEGFR2. In some embodiments, the selectivity is 2-fold or more, 3-fold or more, 5-fold or more, 10-fold or more, 50-fold or more, or 100-fold or more.

As FGFR inhibitors, the compounds of the invention are useful in the treatment of various diseases associated with abnormal expression or activity of FGFR enzymes or FGFR ligands.

For example, the compounds of the invention are useful in the treatment of cancer. Example cancers include bladder cancer, breast cancer, cervical cancer, colorectal cancer,

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endometrial cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas), ovarian cancer, prostate cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (e.g. exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, skin cancer (e.g., squamous cell carcinoma).

Further example cancers include hematopoietic malignancies such as leukemia, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, myeloproliferative neoplasms (e.g., polycythemia vera, essential thrombocythemia, and primary myelofibrosis), Waldenstrom's Macroglobulinemia, hairy cell lymphoma, and Burkett's lymphoma.

Other cancers treatable with the compounds of the invention include glioblastoma, melanoma, and rhabdomyosarcoma.

In addition to oncogenic neoplasms, the compounds of the invention can be useful in the treatment of skeletal and chondrocyte disorders including, but not limited to, achondroplasia, hypochondroplasia, dwarfism, thanatophoric dysplasia (TD) (clinical forms TD I and TD II), Apert syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, and craniosynostosis syndromes.

The compounds of the invention may further be useful in the treatment of fibrotic diseases, such as where a disease symptom or disorder is characterized by fibrosis. Example fibrotic diseases include liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, and wound healing.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the FGFR enzyme with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having FGFR, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the FGFR enzyme.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein the term "treating" or "treatment" refers to 1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; 2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), or 3) ame-

liorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

Combination Therapy

One or more additional pharmaceutical agents or treatment methods such as, for example, anti-viral agents, chemotherapeutics or other anti-cancer agents, immune enhancers, immunosuppressants, radiation, anti-tumor and anti-viral vaccines, cytokine therapy (e.g., IL2, GM-CSF, etc.), and/or tyrosine kinase inhibitors can be used in combination with the compounds of the present invention for treatment of FGFR-associated diseases, disorders or conditions. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

Suitable antiviral agents contemplated for use in combination with the compounds of the present invention can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

Example suitable NRTIs include zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil[bis (POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emtricitabine[(-)—FTC]; beta-L-FD4 (also called beta-L-D4C and named beta-L-2',3'-dideoxy-5-fluoro-cytidine); DAPD, ((-)-beta-D-2,6,-diamino-purine dioxolane); and lodenosine (FddA). Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4(1H,3H)-pyrimidinedione); and (+)-calanolide A (NSC-675451) and B. Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfinavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1549. Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No. 11607.

Suitable chemotherapeutic or other anti-cancer agents include, for example, alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazines) such as uracil mustard, chlormethine, cyclophosphamide (CytosanTM), ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide.

Other suitable agents for use in combination with the compounds of the present invention include: dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen," which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC; or temozolomide. Compounds according to the invention may also be combined with immunotherapy drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF) in.

Suitable chemotherapeutic or other anti-cancer agents include, for example, antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) such as methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatin, and gemcitabine.

Suitable chemotherapeutic or other anti-cancer agents further include, for example, certain natural products and their derivatives (for example, vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epidophyllotoxins) such as vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (TAXOLTM), mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, interferons (especially IFN- α), etoposide, and teniposide.

Other cytotoxic agents include navelbene, CPT-11, anastrozole, letrozole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

Also suitable are cytotoxic agents such as epidophyllo-toxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4, 4-1BB and PD-1, or antibodies to cytokines (IL-10, TGF- β , etc.).

Other anti-cancer agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4.

Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer.

Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, N.J.), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions which refers to a combination of a compound of the invention, or its pharmaceutically acceptable salt, and at least one pharmaceutically acceptable carrier. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and pow-

ders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the invention above in combination with one or more pharmaceutically acceptable carriers. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these pre-formulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage

forms such as tablets, pills and capsules. This solid pre-formulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in

a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

The compounds of the invention can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as antiviral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like. Labeled Compounds and Assay Methods

Another aspect of the present invention relates to fluorescent dye, spin label, heavy metal or radio-labeled compounds of the invention that would be useful not only in imaging but also in assays, both in vitro and in vivo, for localizing and quantitating the FGFR enzyme in tissue samples, including human, and for identifying FGFR enzyme ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes FGFR enzyme assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ²H (also written as D for deuterium), ³H (also written as T for tritium), ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶Cl, ⁸²Br, ⁷⁵Br, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I, ¹²⁵I and ¹³¹I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for in vitro FGFR enzyme labeling and competition assays, compounds that incorporate ³H, ¹⁴C, ⁸²Br, ¹²⁵I, ¹³¹I, or ³⁵S will generally be most useful. For radio-imaging applications ¹¹C, ¹⁸F, ¹²⁵I, ¹²³I, ¹²⁴I, ¹³¹I, ⁷⁵Br, ⁷⁶Br or ⁷⁷Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ³H, ¹⁴C, ¹²⁵I, ³⁵S and ⁸²Br.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art.

A radio-labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the radio-labeled compound of the invention to the FGFR enzyme. Accordingly, the ability of a test compound to compete with the radio-labeled compound for binding to the FGFR enzyme directly correlates to its binding affinity. Kits

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of FGFR-

associated diseases or disorders, obesity, diabetes and other diseases referred to herein which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples were found to be inhibitors of one or more FGFR's as described below.

EXAMPLES

Experimental procedures for compounds of the invention are provided below. Preparatory LC-MS purifications of some of the compounds prepared were performed on Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in the literature. See e.g. "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, 4, 295 (2002); "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Hague, A. Combs, *J. Combi. Chem.*, 5, 670 (2003); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Combi. Chem.*, 6, 874-883 (2004). The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity check under the following conditions: Instrument; Agilent 1100 series, LC/MSD, Column: Waters Sunfire™ C₁₈ 5 µm, 2.1×5.0 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: 0.025% TFA in acetonitrile; gradient 2% to 80% of B in 3 minutes with flow rate 1.5 mL/minute.

Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

pH=2 purifications: Waters Sunfire™ C₁₈ 5 µm, 19×100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: 0.1% TFA in acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [see "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, 6, 874-883 (2004)]. Typically, the flow rate used with the 30×100 mm column was 60 mL/minute.

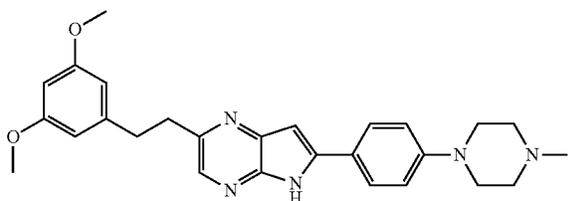
pH=10 purifications: Waters XBridge C₁₈ 5 µm, 19×100 mm column, eluting with mobile phase A: 0.15% NH₄OH in water and mobile phase B: 0.15% NH₄OH in acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [See "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R.

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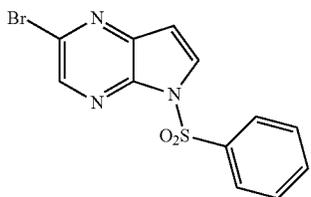
Sparks, A. Combs, *J. Comb. Chem.*, 6, 874-883 (2004). Typically, the flow rate used with 30x100 mm column was 60 mL/minute.

Example 1

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine

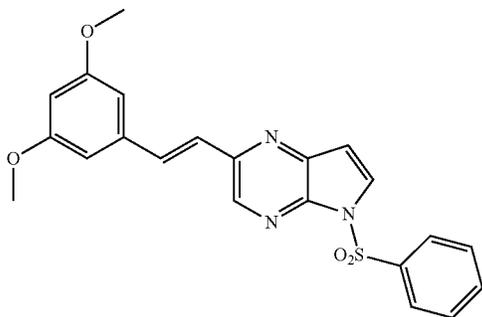


Step 1. 2-bromo-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



To a stirred solution of 2-bromo-5H-pyrrolo[2,3-b]pyrazine (from Ark Pharm, cat# AK-23813, 1.00 g, 5.05 mmol) in tetrahydrofuran (10 mL), NaH (60% w/w dispersion form in mineral oil, 283 mg, 7.07 mmol) was added at 0° C. After 0.5 hour, benzenesulfonyl chloride (644 μL, 5.05 mmol) was added dropwise. After another 1 hour, the reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with methylene chloride. The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified on silica gel (eluting with 0 to 50% ethyl acetate (EtOAc) in hexanes) to give the desired product (1.50 g, 88%). LCMS calculated for C₁₂H₉BrN₃O₂S (M+H)⁺: m/z=339.2. Found: 339.2.

Step 2. 2-[(E)-2-(3,5-dimethoxyphenyl)vinyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine

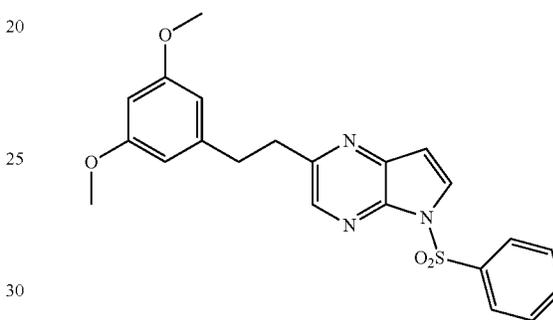


A stirred mixture of 2-bromo-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (929 mg, 2.75 mmol), 2-[(E)-2-(3,5-

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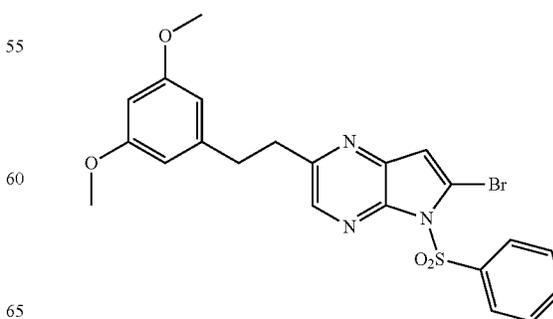
dimethoxyphenyl)vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (from Aldrich, cat#676160, 838 mg, 2.89 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with dichloromethane (1:1) (140 mg, 0.171 mmol), and potassium phosphate (1.20 g, 5.65 mmol) in 1,4-dioxane (20 mL)/water (9.6 mL) was heated at 88° C. After 1 hour, the reaction mixture was quenched with saturated aq. NH₄Cl and extracted with methylene chloride. The combined organic layers were dried over MgSO₄, filtered, and then concentrated. The residue was purified on silica gel (eluting with 0 to 50% EtOAc in hexanes) to give the desired product (1.10 g, 95%). LCMS calculated for C₂₂H₂₀N₃O₄S (M+H)⁺: m/z=422.2. Found: 422.2.

Step 3. 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



To a stirred solution of 2-[(E)-2-(3,5-dimethoxyphenyl)vinyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (1.10 g, 2.61 mmol) in tetrahydrofuran (8 mL)/methanol (10 mL), was added Pd/C (10% w/w, 580 mg, 0.545 mmol). The resulted mixture was stirred under H₂ (45 psi) at ambient temperature. After 24 hours, the palladium catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to afford the desired product (1.05 g, 90%), which was used directly in the next step without further purification. LCMS calculated for C₂₂H₂₂N₃O₄S (M+H)⁺: m/z=424.2. Found: 424.2; ¹H NMR (400 MHz, CDCl₃): δ 8.18-8.15 (m, 3H), 7.97 (d, J=4.4 Hz, 1H), 7.63-7.59 (m, 1H), 7.53-7.48 (m, 2H), 6.80 (d, J=4.4 Hz, 1H), 6.34 (d, J=2.0 Hz, 2H), 6.30 (t, J=2.4 Hz, 1H), 3.73 (s, 6H), 3.19-3.15 (m, 2H), 3.02-2.98 (m, 2H) ppm.

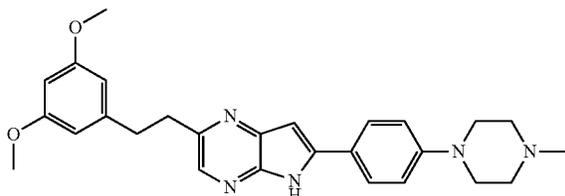
Step 4. 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



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To a stirred solution of N,N-diisopropylamine (0.610 mL, 4.25 mmol) in tetrahydrofuran (2.0 mL) at -78°C ., n-butyllithium (2.5 M in hexanes, 1.70 mL, 4.25 mmol) was added dropwise. After the white precipitate formed, the mixture was warmed up to 0°C . for 10 minutes. The resulting resulted solution was added to a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (1.30 g, 3.07 mmol) in tetrahydrofuran (10 mL) at 78°C . After 30 min, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (1.10 g, 3.38 mmol) in tetrahydrofuran (6 mL) was added dropwise. After another 1 hour, the reaction mixture was quenched with saturated aq. NH_4Cl , then extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated. The residue was purified on silica gel (eluting with 0 to 50% EtOAc in hexanes) to give the desired product (1.30 g, 84%). LCMS calculated for $\text{C}_{22}\text{H}_{21}\text{BrN}_3\text{O}_4\text{S}$ (M+H)⁺: m/z=502.0. Found: 502.0; ^1H NMR (400 MHz, CDCl_3): δ 8.15-8.12 (m, 3H), 7.68-7.58 (m, 1H), 7.51-7.47 (m, 2H), 6.88 (s, 1H), 6.31 (d, J=2.0 Hz, 2H), 6.28 (t, J=2.5 Hz, 1H), 3.72 (s, 6H), 3.16-3.12 (m, 2H), 2.99-2.96 (m, 2H) ppm.

Step 5. 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine

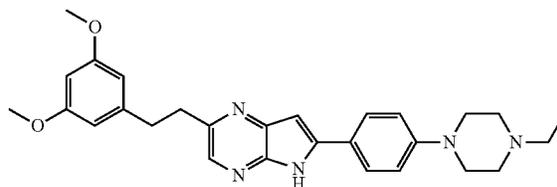


A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (30.0 mg, 59.7 μmol), 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (from Alfa Aesar, cat# H51659, 19.8 mg, 6.57 μmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (4.9 mg, 5.97 μmol), and potassium phosphate (25.4 mg, 119 μmol) in water (0.2 mL)/1,4-dioxane (1 mL) was heated at 88°C . After 1 hour, the volatiles were removed under vacuum and the residue was dissolved in methanol (1 mL). Potassium carbonate (16.5 mg, 119 μmol) was added and the reaction mixture was warmed up to 60°C . After 1 hour, the reaction mixture was cooled to ambient temperature and was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (10.1 mg, 44%) as its (trifluoroacetic acid) TFA salt. LCMS calculated for $\text{C}_{27}\text{H}_{32}\text{N}_5\text{O}_2$ (M+H)⁺: m/z=458.2. Found: 458.2; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.21 (s, 1H), 9.73 (s, 1H), 8.01 (s, 1H), 7.89 (d, J=9.2 Hz, 2H), 7.12 (d, J=9.2 Hz, 2H), 6.93 (d, J=2.0 Hz, 1H), 6.38 (d, J=2.4 Hz, 2H), 6.28 (t, J=2.4 Hz, 1H), 4.01 (d, J=14.0 Hz, 2H), 3.67 (s, 6H), 3.52 (d, J=12.8 Hz, 2H), 3.19-2.93 (m, 8H), 2.86 (d, J=4.0 Hz, 3H) ppm.

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Example 2

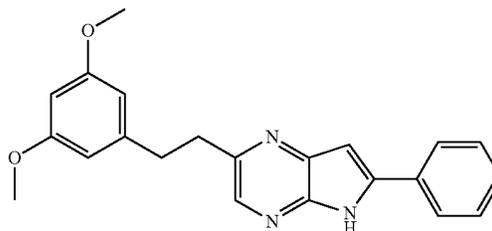
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-ethylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1-ethyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (from Ark Pharm, cat# AK-40362) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $\text{C}_{28}\text{H}_{34}\text{N}_5\text{O}_2$ (M+H)⁺: m/z=472.3. Found: 472.3.

Example 3

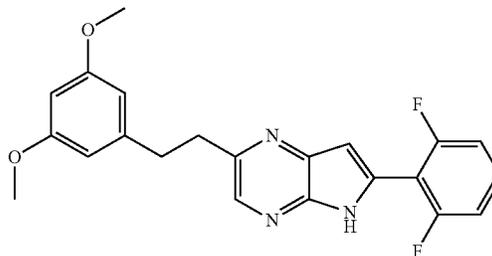
2-(3,5-dimethoxyphenethyl)-6-phenyl-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with phenylboronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $\text{C}_{22}\text{H}_{22}\text{N}_3\text{O}_2$ (M+H)⁺: m/z=360.2. Found: 360.2.

Example 4

6-(2,6-difluorophenyl)-2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazine

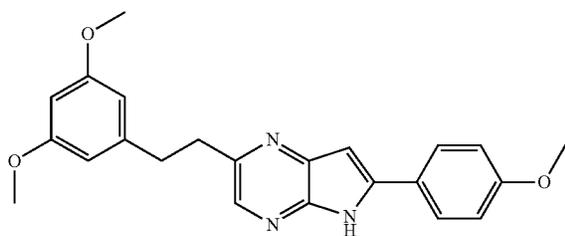


This compound was prepared using procedures analogous to those for Example 1, Step 5, with 2,6-difluorophenylboronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $\text{C}_{22}\text{H}_{20}\text{F}_2\text{N}_3\text{O}_2$ (M+H)⁺: m/z=396.2. Found: 396.1.

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Example 5

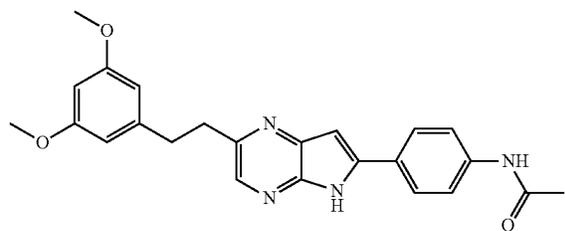
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(4-methoxyphenyl)-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with (4-methoxyphenyl)boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{24}N_3O_3$ (M+H)⁺: m/z=390.2. Found: 390.2; ¹H NMR (300 MHz, CDCl₃): δ 9.90 (s, 1H), 7.90 (s, 1H), 7.63 (d, J=8.7 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 6.78 (d, J=1.8 Hz, 1H), 6.33 (d, J=2.4 Hz, 2H), 6.23 (t, J=2.4 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 6H), 3.15-3.10 (m, 2H), 3.02-2.97 (m, 2H) ppm.

Example 6

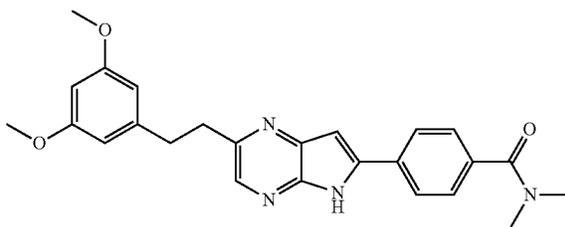
N-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}phenyl)acetamide



This compound was prepared using procedures analogous to those for Example 1, Step 5, with [4-(acetlamino)phenyl]boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{24}H_{25}N_4O_3$ (M+H)⁺: m/z=417.2. Found: 417.2.

Example 7

4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-dimethylbenzamide



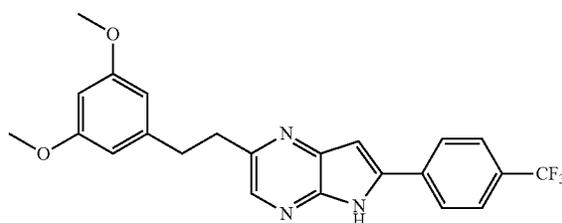
This compound was prepared using procedures analogous to those for Example 1, Step 5, with {4-[(dimethylamino)carbonyl]phenyl}boronic acid replacing 1-methyl-4-[4-(4,4,

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5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{25}H_{27}N_4O_3$ (M+H)⁺: m/z=431.2. Found: 431.2.

Example 8

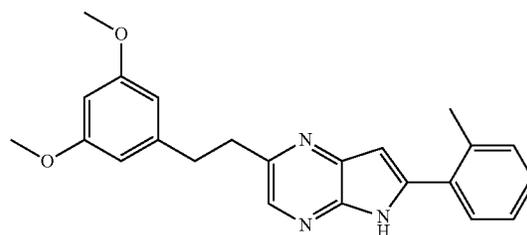
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(trifluoromethyl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with (4-trimethylphenyl)boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{21}F_3N_3O_2$ (M+H)⁺: m/z=428.2. Found: 428.1.

Example 9

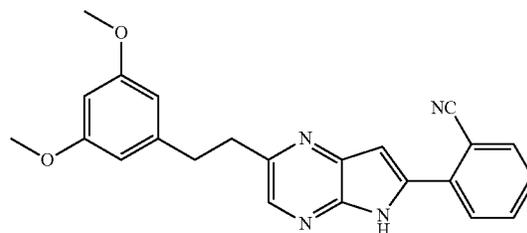
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(2-methylphenyl)-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with (2-methylphenyl)boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{24}N_3O_2$ (M+H)⁺: m/z=374.2. Found: 374.2.

Example 10

2-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}benzotrile

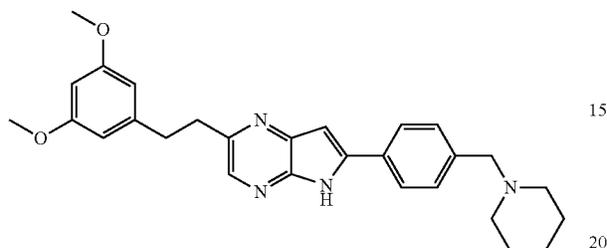


39

This compound was prepared using procedures analogous to those for Example 1, Step 5, with (2-cyanophenyl)boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{21}N_4O_2$ (M+H)⁺: m/z=385.2. Found: 385.2.

Example 11

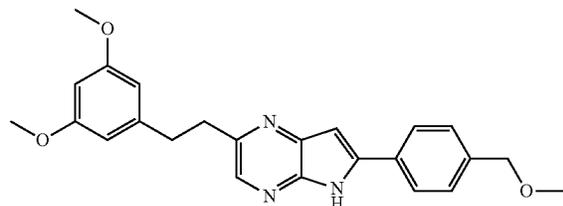
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(piperidin-1-ylmethyl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]piperidine (from Frontier, cat# P10017) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{28}H_{33}N_4O_2$ (M+H)⁺: m/z=457.2. Found: 457.3.

Example 12

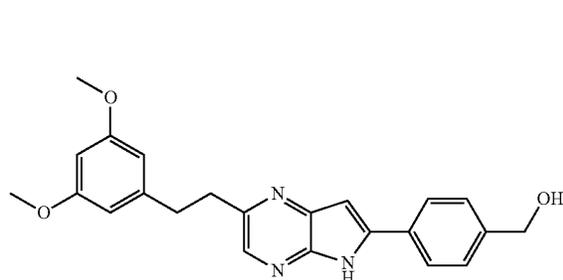
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(methoxymethyl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with [4-(methoxymethyl)phenyl]boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{24}H_{26}N_3O_3$ (M+H)⁺: m/z=404.2. Found: 404.2.

Example 13

(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}phenyl)methanol



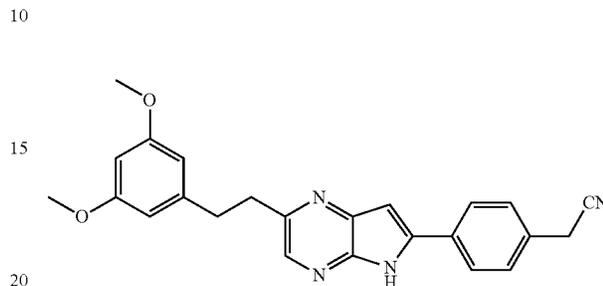
This compound was prepared using procedures analogous to those for Example 1, Step 5, with 4-hydroxymethylben-

40

zeneboronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{24}N_3O_3$ (M+H)⁺: m/z=390.2. Found: 390.1.

Example 14

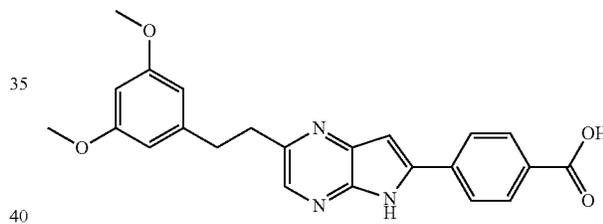
(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}phenyl)acetonitrile



This compound was prepared using procedures analogous to those for Example 1, Step 5, with [4-(cyanomethyl)phenyl]boronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{24}H_{23}N_4O_2$ (M+H)⁺: m/z=399.2. Found: 399.2.

Example 15

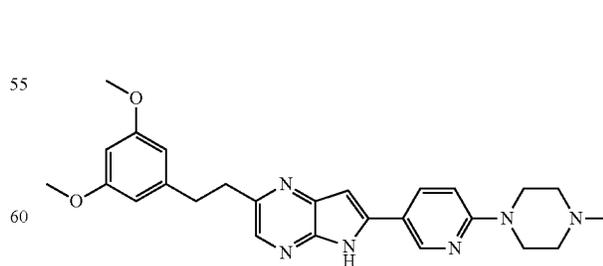
4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}benzoic acid



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 4-(dihydroxyboryl)benzoic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{22}N_3O_4$ (M+H)⁺: m/z=404.2. Found: 404.2.

Example 16

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-5H-pyrrolo[2,3-b]pyrazine



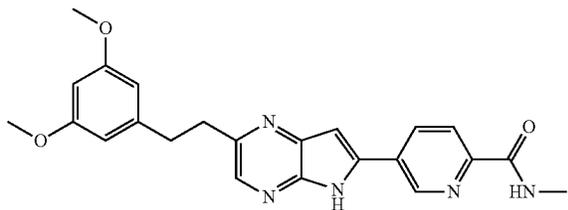
This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine (from Frontier, cat# P1824) replacing 1-methyl-4-[4-

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4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{26}H_{21}N_6O_2$ (M+H)⁺: $m/z=459.2$. Found: 459.3.

Example 17

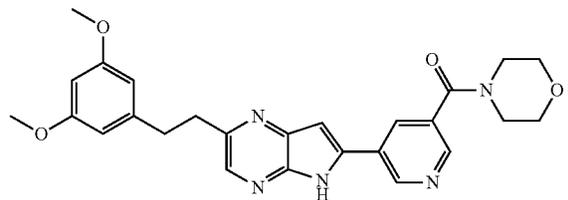
5-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N-methylpyridine-2-carboxamide



This compound was prepared using procedures analogous to those for Example 1, Step 5, with {6-[(methylamino)carbonyl]pyridin-3-yl}boronic acid (from Frontier, cat# M10074) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{24}N_5O_3$ (M+H)⁺: $m/z=418.2$. Found: 418.3.

Example 18

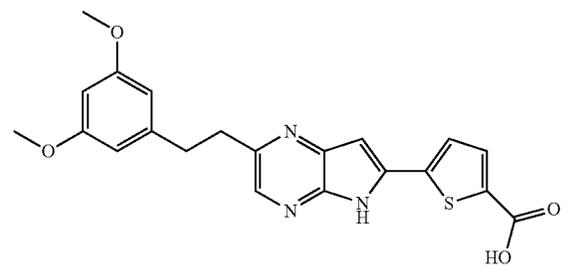
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[5-(morpholin-4-ylcarbonyl)pyridin-3-yl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 4-{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl]carbonyl}morpholine (from Frontier, cat# M1818) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{26}H_{28}N_5O_4$ (M+H)⁺: $m/z=474.2$. Found: 474.2.

Example 19

4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}thiophene-2-carboxylic acid



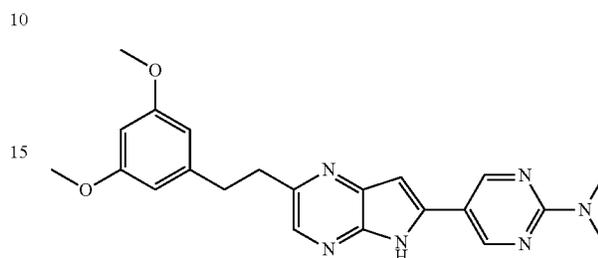
This compound was prepared using procedures analogous to those for Example 1, Step 5, with 4-(dihydroxyboryl)thiophene-2-carboxylic acid (from Frontier, cat# C1695)

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replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{21}H_{20}N_3O_4S$ (M+H)⁺: $m/z=410.1$. Found: 410.1.

Example 20

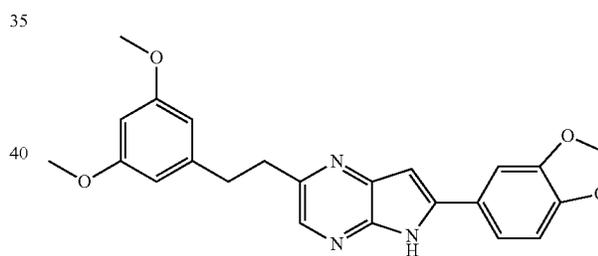
5-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-dimethylpyrimidin-2-amine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (from Frontier, cat# D1773) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{22}H_{25}N_6O_2$ (M+H)⁺: $m/z=405.2$. Found: 405.2.

Example 21

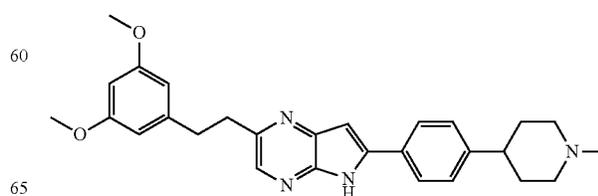
6-(1,3-benzodioxol-5-yl)-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1,3-benzodioxol-5-ylboronic acid replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{23}H_{22}N_3O_4$ (M+H)⁺: $m/z=404.2$. Found: 404.2.

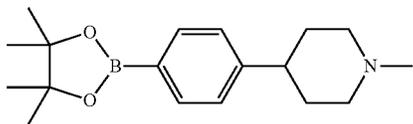
Example 22

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(1-methylpiperidin-4-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



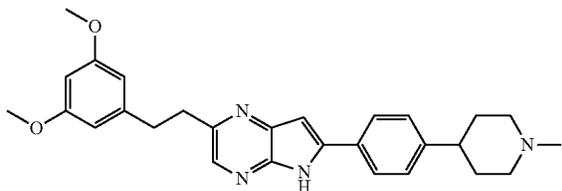
43

Step 1. 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine



To a stirred solution of 4-(4-bromophenyl)-1-methylpiperidine (from J&W PharmLab, cat#60-0498, 200 mg, 0.787 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.210 g, 0.826 mmol) in 1,4-dioxane (1.62 mL, 20.7 mmol) [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (27.0 mg, 33.1 μ mol), potassium acetate (0.160 g, 1.63 mmol), and 1,1'-bis(diphenylphosphino)ferrocene (19.0 mg, 3.43 μ mol) was added sequentially. The reaction mixture was then warmed up to 90° C. After 3 hours, the reaction mixture was quenched with saturated aq. NH_4Cl , extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated to give the desired product (190 mg, 80%). LCMS calculated for $\text{C}_{18}\text{H}_{29}\text{BNO}_2$ (M+H)⁺: $m/z=302.2$. Found: 302.2.

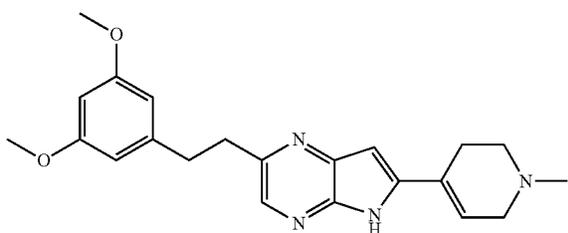
Step 2. 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(1-methylpiperidin-4-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine (from Example 22, Step 1) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $\text{C}_{28}\text{H}_{33}\text{N}_4\text{O}_2$ (M+H)⁺: $m/z=457.3$. Found: 457.2.

Example 23

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine

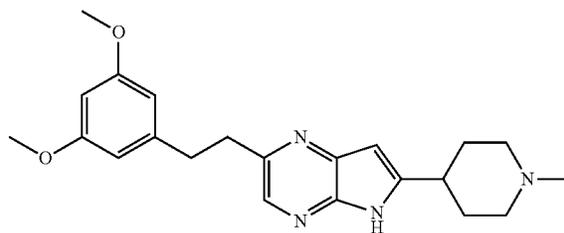


44

This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $\text{C}_{22}\text{H}_{27}\text{N}_4\text{O}_2$ (M+H)⁺: $m/z=379.2$. Found: 379.3.

Example 24

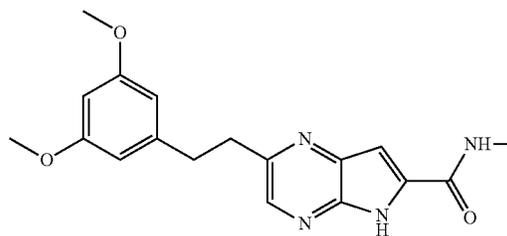
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methylpiperidin-4-yl)-5H-pyrrolo[2,3-b]pyrazine



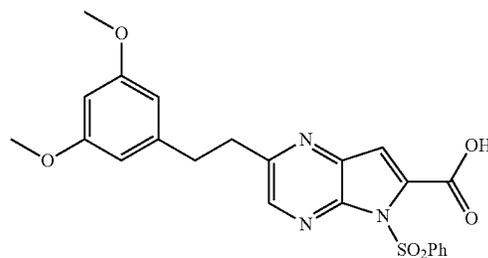
To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine (from Example 23, 10 mg, 26.4 μ mol) in methanol (1 mL), Pd/C (10% w/w, 3.2 mg, 3.0 μ mol) was added. The reaction mixture was then stirred under the atmosphere of H_2 at ambient temperature. After 3 hours, the palladium catalyst was filtered and the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.0 mg, 30%) as its TFA salt. LCMS calculated for $\text{C}_{22}\text{H}_{29}\text{N}_4\text{O}_2$ (M+H)⁺: $m/z=381.2$. Found: 381.3.

Example 25

2-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide



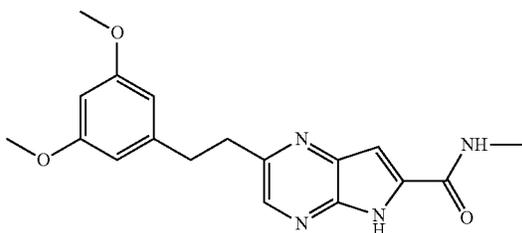
Step 1. 2-(3,5-dimethoxyphenethyl)-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine-6-carboxylic acid



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To a stirred solution of N,N-diisopropylamine (64.8 μ L, 0.463 mmol) in tetrahydrofuran (0.3 mL) at -78° C., n-butyllithium (2.5 M in hexanes, 0.185 mL, 0.463 mmol) was added dropwise. After the white precipitate formed, the reaction mixture was warmed up to 0° C. for 10 minutes. The resulted solution was transferred to a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from example 1, step 4, 130 mg, 0.310 mmol) in tetrahydrofuran (2 mL) at 78° C. A dark red solution was formed. After 15 minutes, dry CO_2 (prepared by passing CO_2 through drying tube) was bubbled into the reaction mixture. After another 15 minutes, the reaction mixture was quenched with saturated aq. NH_4Cl , extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated to afford the desired product (135 mg, 94%). LCMS calculated for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_6\text{S}$ ($\text{M}+\text{H}$) $^{+}$: $m/z=468.1$. Found: 468.0.

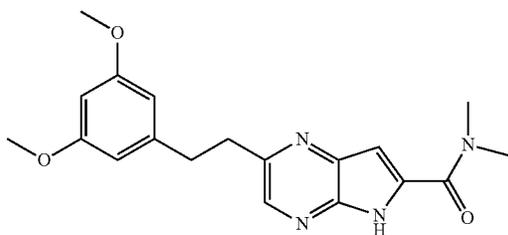
Step 2. 2-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide



To a stirred solution of 2-(3,5-dimethoxyphenyl)-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine-6-carboxylic acid (27 mg, 57.8 μ mol) in N,N-dimethylformamide (2 mL), methylamine (2.0 M in THF, 57.8 μ L, 0.116 mmol), HATU (43.9 mg, 0.116 mmol) and N,N-diisopropylethylamine (40.2 μ L, 0.231 mmol) were added sequentially at ambient temperature. After 1 hour, the reaction was quenched with saturated aq. NH_4Cl , then extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated. The residue was dissolved in methanol (2.0 mL), and potassium carbonate (16.0 mg, 0.116 mmol) was added. The reaction mixture was then warmed up to 60° C. After 1 hour, the crude mixture was allowed to warm to room temperature and was then purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at a flow rate of 30 mL/min) to give the desired product (6.0 mg, 30%) as its TFA salt. LCMS calculated for $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O}_3$ ($\text{M}+\text{H}$) $^{+}$: $m/z=341.2$. Found: 341.1.

Example 26

2-[2-(3,5-dimethoxyphenyl)ethyl]-N,N-dimethyl-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide

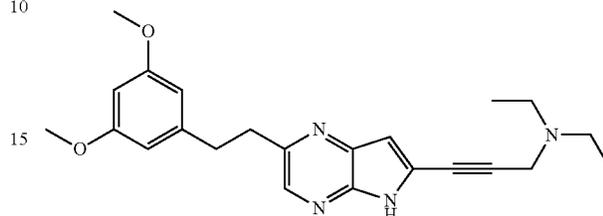


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This compound was prepared using procedures analogous to those for Example 15, Step 2, with dimethylamine (2.0 M in THF) replacing methylamine (2.0 M in THF). LCMS calculated for $\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^{+}$: $m/z=355.2$. Found: 355.2.

Example 27

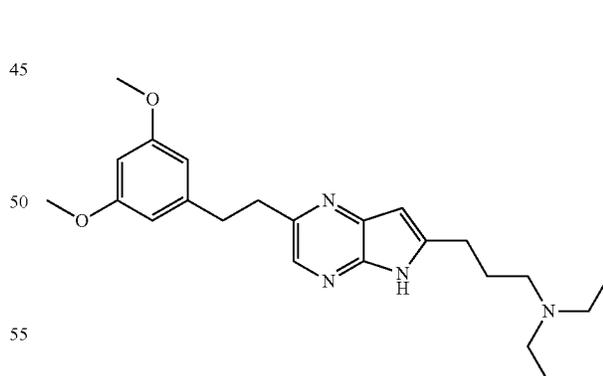
3-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-diethylprop-2-yn-1-amine



A solution of N,N-diethylprop-2-yn-1-amine (10.6 mg, 95.5 μ mol), bis(triphenylphosphine)palladium(II) chloride (2.8 mg, 4.0 μ mol), copper(I) iodide (1.2 mg, 6.4 mmol), triethylamine (17.0 μ L, 120 μ mol), and 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from Example 1, Step 4, 40.0 mg, 79.7 μ mol) in N,N-dimethylformamide (1.0 mL) was stirred at ambient temperature overnight. The reaction was quenched with saturated aq. NH_4Cl , then extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated. The residue was dissolved in methanol (2.0 mL) and potassium carbonate (22.0 mg, 0.159 mmol) was added. The reaction mixture was then warmed up to 60° C. After 1 hour, the crude mixture was allowed to warm to room temperature and was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (6.0 mg, 20%) as its TFA salt. LCMS calculated for $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^{+}$: $m/z=393.2$. Found: 393.1.

Example 28

3-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-diethylpropan-1-amine



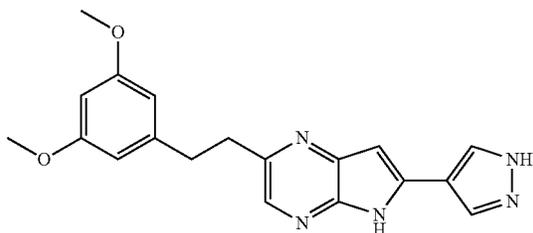
To a stirred solution of 3-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-diethylprop-2-yn-1-amine (from Example 27, 5 mg, 12.7 μ mol) in methanol (2 mL), Pd/C (10% w/w, 5.0 mg, 4.7 μ mol) was added. The resulted mixture was stirred under H_2 at ambient temperature. After 1.5 hours, the palladium catalyst was filtered and the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired

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product (2.4 mg, 50%) as its TFA salt. LCMS calculated for $C_{23}H_{33}N_4O_2$ (M+H)⁺: m/z=397.3. Found: 397.3.

Example 29

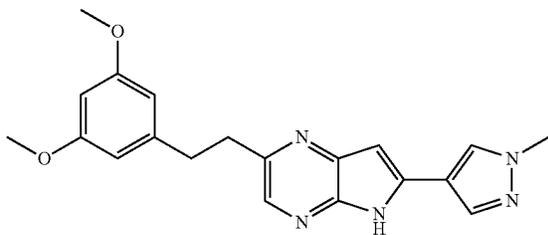
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{19}H_{20}N_5O_2$ (M+H)⁺: m/z=350.2. Found: 350.2.

Example 30

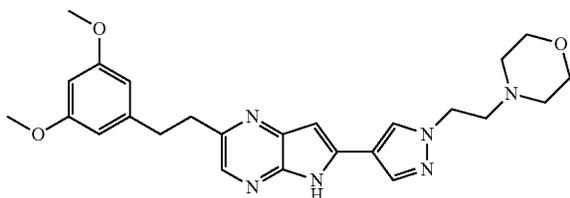
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 1, Step 5, with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{20}H_{22}N_5O_2$ (M+H)⁺: m/z=364.2. Found: 364.2.

Example 31

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine



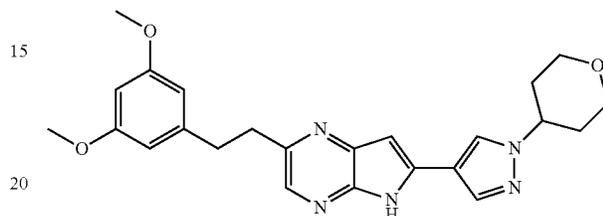
This compound was prepared using procedures analogous to those for Example 1, Step 5, with 4-[2-[4-(4,4,5,5-tetramethyl-

48

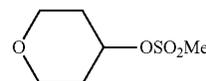
ethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]ethyl]morpholine (from Combi-Blocks, cat# PN-8727) replacing 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{25}H_{31}N_6O_3$ (M+H)⁺: m/z=463.2. Found: 463.2.

Example 32

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine

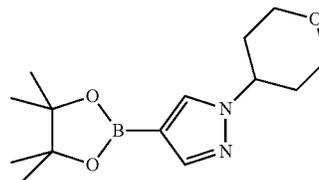


Step 1. tetrahydro-2H-pyran-4-yl methanesulfonate



To a stirred solution of tetrahydro-4H-pyran-4-ol (100.0 μ L, 1.05 mmol) in methylene chloride (8.0 mL) at 0° C., triethylamine (183 μ L, 1.31 mmol) and methanesulfonyl chloride (89.3 μ L, 1.15 mmol) were added sequentially. After 1.5 h, the reaction was quenched with water and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, and then concentrated to give the desired product (190 mg, 100%), which was used directly in the next step. ¹H NMR (400 MHz, $CDCl_3$): δ 4.92-4.87 (m, 1H), 3.97-3.92 (m, 2H), 3.57-3.52 (m, 2H), 3.04 (s, 3H), 2.07-2.02 (m, 2H), 1.92-1.83 (m, 2H) ppm.

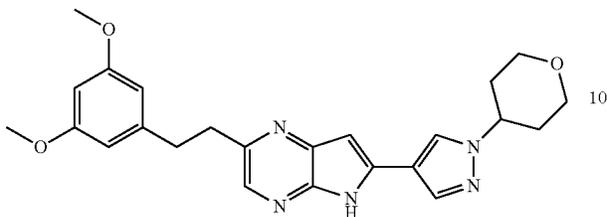
Step 2. 1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (30.0 mg, 0.154 mmol), and tetrahydro-2H-pyran-4-yl methanesulfonate (0.150 g, 0.460 mmol) in acetonitrile (1.0 mL) was stirred at 90° C. for 2 hours. The reaction was quenched with water, extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, then filtered and concentrated under reduced pressure to afford the desired product (35 mg, 80%), which was used directly in the next step without further purification. LCMS calculated for $C_{14}H_{24}BN_2O_3$ (M+H)⁺: m/z=279.2. Found: 279.2.

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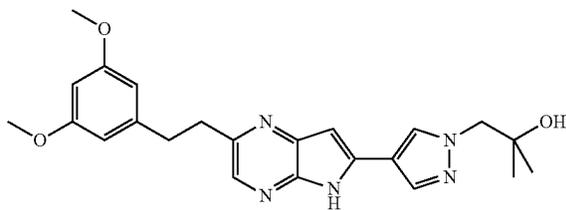
Step 3. 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine



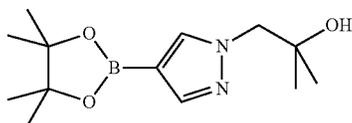
A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (15.0 mg, 29.8 μmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (1.30 mg, 1.59 μmol), 1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.9 mg, 32.0 μmol), and potassium phosphate (13.5 mg, 63.6 μmol) in water (0.2 mL)/1,4-dioxane (0.40 mL) was heated at 88° C. After 1 hour, the volatiles were removed under vacuum and the residues were dissolved in methanol (1 mL). Potassium carbonate (8.8 mg, 63.7 μmol) was added and the reaction mixture was then warmed up to 60° C. After 1 hour, the reaction mixture was cooled to ambient temperature and was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (2.5 mg) as its TFA salt. LCMS calculated for $\text{C}_{24}\text{H}_{28}\text{N}_5\text{O}_3$ ($\text{M}+\text{H}$)⁺: $m/z=434.2$. Found: 434.2.

Example 33

1-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-2-methylpropan-2-ol



Step 1. 2-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]propan-2-ol

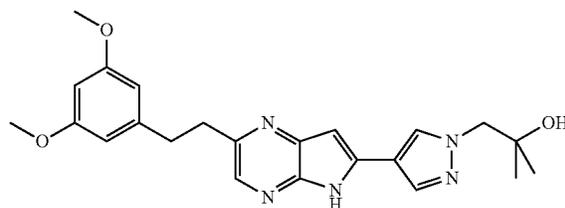


A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (30.0 mg, 0.154 mmol), 2,2-dimethyl-oxirane (25.8 μL , 0.309 mmol), and cesium carbonate (0.150 g,

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0.460 mmol) in acetonitrile (1.0 mL) was stirred at 90° C. for 5 hours. The reaction mixture was cooled to ambient temperature, quenched with water, and extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , then filtered and concentrated under reduced pressure to give the desired product (32 mg, 78%). LCMS calculated for $\text{C}_{13}\text{H}_{24}\text{BN}_2\text{O}_3$ ($\text{M}+\text{H}$)⁺: $m/z=267.2$. Found: 267.2.

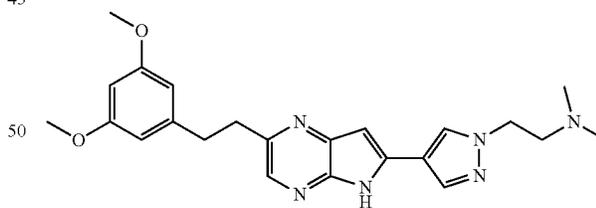
Step 2. 1-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-2-methylpropan-2-ol



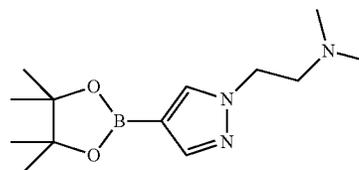
A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from Example 1, Step 5, 15.0 mg, 29.8 μmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) complexed with dichloromethane (1:1) (1.30 mg, 1.59 μmol), 2-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]propan-2-ol (8.5 mg, 31.8 μmol), and potassium phosphate (13.5 mg, 63.7 μmol) in water (0.2 mL)/1,4-dioxane (0.4 mL) was heated at 88° C. After 1 hour, the volatiles were removed under vacuum and the residues were dissolved in methanol (1.0 mL). Potassium carbonate (8.3 mg, 59.7 μmol) was added and the reaction mixture was warmed up to 60° C. After 1 hour, the reaction mixture was cooled to ambient temperature and was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.0 mg) as its TFA salt. LCMS calculated for $\text{C}_{23}\text{H}_{28}\text{N}_5\text{O}_3$ ($\text{M}+\text{H}$)⁺: $m/z=422.2$. Found: 422.3.

Example 34

2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-N,N-dimethylethanamine



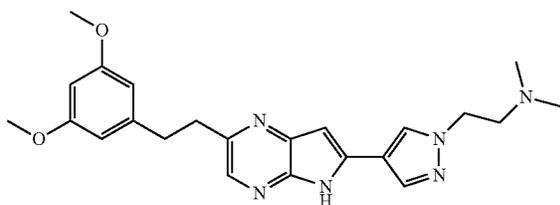
Step 1. N,N-dimethyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]ethanamine



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A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (60.0 mg, 0.309 mmol), β -dimethylaminoethyl chloride hydrochloride (49.0 mg, 0.340 mmol) and cesium carbonate (0.302 g, 0.928 mmol) in acetonitrile (1 mL) was stirred at 90° C. overnight. The reaction mixture was cooled to ambient temperature, quenched with water, and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, then filtered and concentrated under reduced pressure to give the desired product (60 mg, 88%). LCMS calculated for $C_{13}H_{25}BN_3O_2$ (M+H)⁺: m/z=266.2. Found: 266.2.

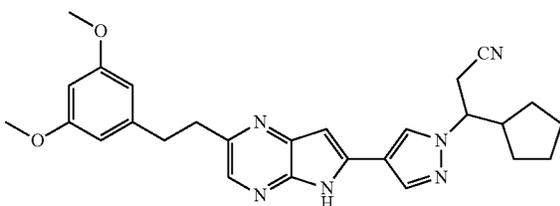
Step 2. 2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-N,N-dimethylethanamine



A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from example 1, step 4, 20.0 mg, 0.0398 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (1.30 mg, 1.59 μ mol), N,N-dimethyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]ethanamine (8.44 mg, 0.0318 mmol), and potassium phosphate (13.5 mg, 0.0637 mmol) in water (0.2 mL)/1,4-dioxane (0.4 mL) was heated at 88° C. After 1 hour, the volatiles were removed under vacuum and the residues were dissolved in methanol (2.0 mL). Potassium carbonate (8.8 mg, 63.7 μ mol) was added and the reaction mixture was warmed up to 60° C. After 1 hour, the reaction mixture was cooled to ambient temperature and was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.0 mg) as its TFA salt. LCMS calculated for $C_{23}H_{29}N_6O_2$ (M+H)⁺: m/z=421.2. Found: 421.2.

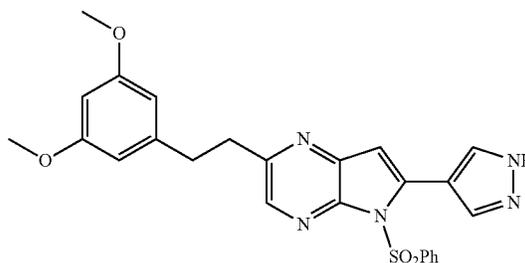
Example 35

3-cyclopentyl-3-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)propanenitrile



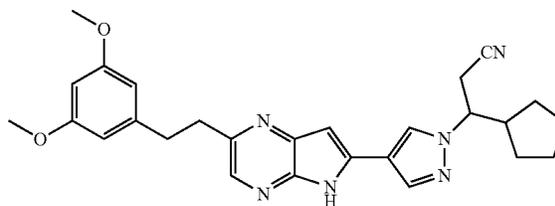
52

Step 1. 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine



A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (180 mg, 0.358 mmol), tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (106 mg, 0.360 mmol), [1,1'-bis(diphenyl-phosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (29.2 mg, 0.0358 mmol), and potassium phosphate (153 mg, 0.719 mmol) in water (2 mL)/1,4-dioxane (5 mL) was heated at 88° C. After 1 hour, the reaction mixture was cooled to ambient temperature, quenched with water, and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, and then concentrated. The residue was purified on silica gel (eluting with 0 to 50% EtOAc in hexanes) to give the desired product (132 mg, 75%). LCMS calculated for $C_{25}H_{24}N_5O_4S$ (M+H)⁺: m/z=490.2. Found: 490.2.

Step 2. 3-cyclopentyl-3-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)propanenitrile

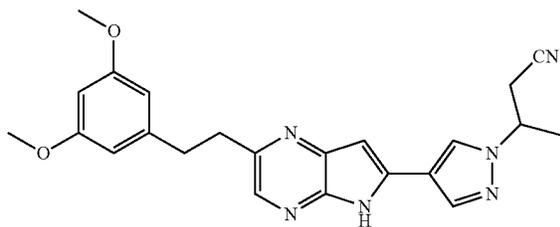


To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine (25.0 mg, 51.1 μ mol) in acetonitrile (1.0 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (9.2 μ L, 61.5 μ mol) and (2E)-3-cyclopentylacrylonitrile (from Adesis, cat#9-245, 6.8 μ L, 61.7 μ mol) were added sequentially at room temperature. After 16 hours, the volatiles were removed and the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (4.2 mg) as its TFA salt. LCMS calculated for $C_{27}H_{31}N_6O_2$ (M+H)⁺: m/z=471.2. Found: 471.2.

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Example 36

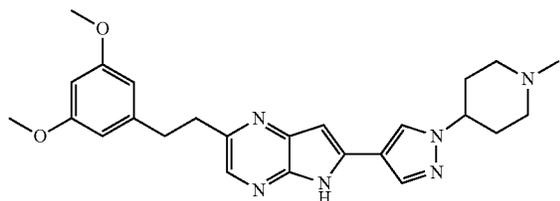
3-(4-(2-(3,5-dimethoxyphenyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)butanenitrile



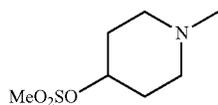
This compound was prepared using procedures analogous to those for Example 35, Step 2, with 2-butenitrile replacing (2E)-3-cyclopentylacrylonitrile. LCMS calculated for $C_{23}H_{25}N_6O_2$ (M+H)⁺: m/z=417.2. Found: 417.2.

Example 37

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine



Step 1. 1-methylpiperidin-4-yl methanesulfonate

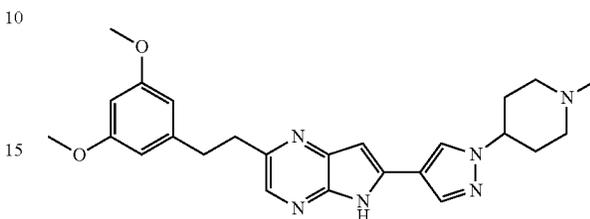


4-Hydroxy-N-methylpiperidine (200 μ L, 1.70 mmol) was dissolved in methylene chloride (10 mL) and then cooled to 0° C. Triethylamine (296 μ L, 2.13 mmol) was added, followed by the addition of methanesulfonyl chloride (145 μ L, 1.87 mmol). After 1.5 hours, the reaction was quenched with water, and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, then concentrated

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under vacuum to give the desired product (280 mg, 88%). LCMS calculated for $C_7H_{16}NO_3S$ (M+H)⁺: m/z=194.1. Found: 194.1.

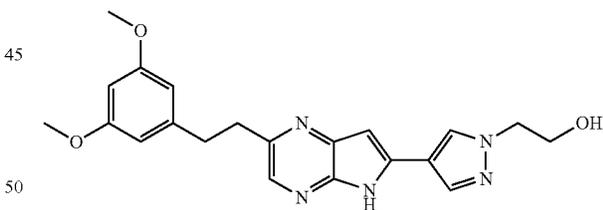
5 Step 2. 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine



20 To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine (from Example 35, Step 1, 50.0 mg, 0.102 mmol) in N,N-dimethylformamide (2.0 mL), sodium hydride (6.13 mg, 0.153 mmol) was added at 0° C. After 15 minutes, a solution of 1-methylpiperidin-4-yl methanesulfonate (23.7 mg, 0.122 mmol) in N,N-dimethylformamide (1 mL) was added. The reaction mixture was then warmed up to 55° C. After 2 hours, the reaction was quenched with water, and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, then filtered and concentrated. The crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (2.2 mg) as its TFA salt. LCMS calculated for $C_{25}H_{31}N_6O_2$ (M+H)⁺: m/z=447.3. Found: 447.3.

Example 38

2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)ethanol



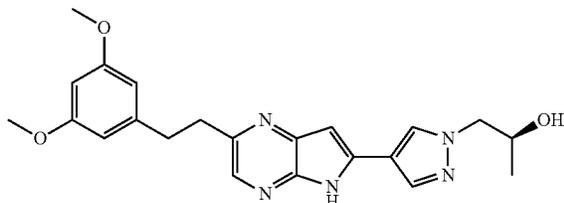
To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine (from Example 35, Step 1, 30.0 mg, 0.0613 mmol) in acetonitrile (1 mL), cesium carbonate (20.0 mg, 0.0613 mmol) and (2-bromoethoxy) (tert-butyl)dimethylsilane (13.1 μ L, 0.0613 mmol) were added sequentially at ambient temperature. The reaction mixture was then warmed up to 60° C. After 2 hours, the reaction was quenched with water, and extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, concentrated. The residue was dissolved in methylene chloride (1.0 mL) and trifluoroacetic acid (1.0 mL) at ambient temperature. After 2 hours, the volatiles were removed under vacuum and the residues were dissolved in methanol (2.0 mL). Potassium carbonate (16.9 mg, 0.122 mmol) was added and the reaction mixture was warmed up to

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60° C. After 1 hour, the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.5 mg) as its TFA salt. LCMS calculated for $C_{21}H_{24}N_5O_3$ (M+H)⁺: m/z=394.2. Found: 394.2.

Example 39

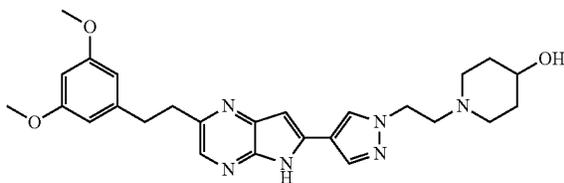
(2S)-1-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl]-1H-pyrazol-1-yl}propan-2-ol



To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine (from Example 35, Step 1, 30.0 mg, 0.0613 mmol) and (S)-(-)-methyloxirane (8.56 μ L, 0.122 mmol) in isopropyl alcohol (2 mL)/N,N-dimethylformamide (0.5 mL), triethylamine (17.1 μ L, 0.122 mmol) was added at ambient temperature. The reaction mixture was then warmed up to 90° C. After 2 hours, the volatiles were removed and the residue was dissolved in methanol (2 mL). Potassium carbonate (16.9 mg, 0.122 mmol) was added and the reaction mixture was warmed up to 60° C. After 30 minutes, the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.8 mg) as its TFA salt. LCMS calculated for $C_{22}H_{26}N_5O_3$ (M+H)⁺: m/z=408.2. Found: 408.2.

Example 40

1-[2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl]-1H-pyrazol-1-yl}ethyl)piperidin-4-ol



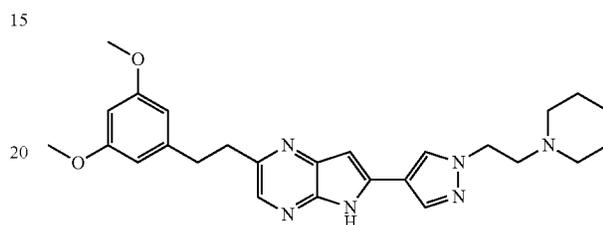
To a stirred solution of 1-piperidineethanol (7.9 mg, 0.0613 mmol) and triphenylphosphine (16.1 mg, 0.0613 mmol) in tetrahydrofuran (1.0 mL), diethyl azodicarboxylate (9.65 μ L, 0.0613 mmol) was added at ambient temperature. After 15 minutes, a solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine (from Example 35, Step 1, 25 mg, 0.0510 mmol) in tetrahydrofuran (0.5 mL) was added. After 16 hours, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with methylene chloride. The combined organic layers were dried over $MgSO_4$, and then concentrated. The residue was dissolved in methanol (2 mL) and potassium carbonate (14.1 mg, 0.102 mmol) was added. The reaction

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mixture was then warmed up to 60° C. After 30 minutes, the crude mixture was cooled to ambient temperature and purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.2 mg) as its TFA salt. LCMS calculated for $C_{26}H_{33}N_6O_3$ (M+H)⁺: m/z=477.3. Found: 477.2.

Example 41

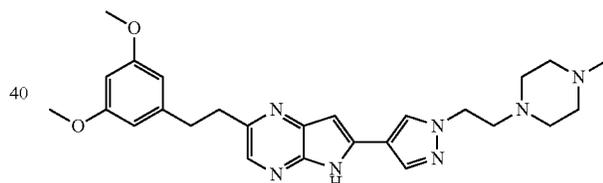
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(2-piperidin-1-ylethyl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 40, with 2-(piperidin-1-yl)ethanol replacing 1-piperidineethanol. LCMS calculated for $C_{26}H_{33}N_6O_2$ (M+H)⁺: m/z=461.3. Found: 461.2.

Example 42

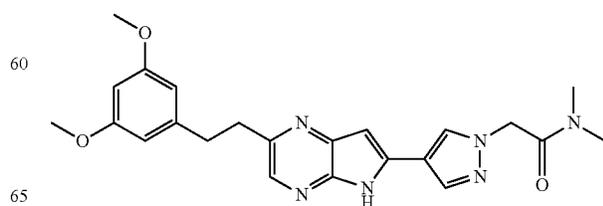
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-{1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 40, with 2-(4-methylpiperazin-1-yl)ethanol replacing 1-piperidineethanol. LCMS calculated for $C_{26}H_{34}N_7O_2$ (M+H)⁺: m/z=476.3. Found: 476.2.

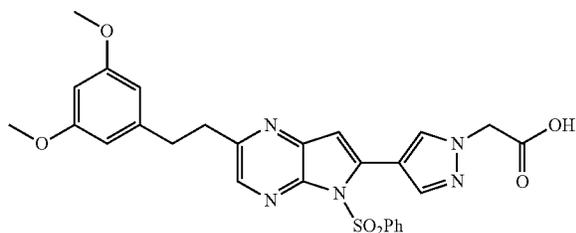
Example 43

2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl]-1H-pyrazol-1-yl)-N,N-dimethylacetamide



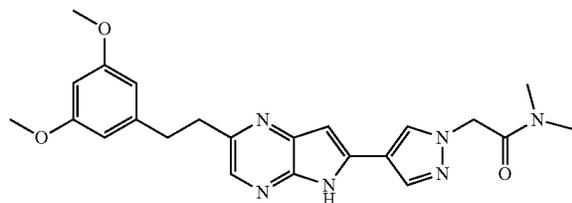
57

Step 1. {4-[2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]-1H-pyrazol-1-yl}acetic acid



A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from Example 1, Step 4, 40.0 mg, 79.7 μ mol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (3.25 mg, 3.98 μ mol), tert-butyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]acetate (24.5 mg, 79.6 μ mol), and potassium phosphate (33.8 mg, 0.159 mmol) in water (0.5 mL)/1,4-dioxane (1.0 mL) was heated at 88° C. After 1 hour, the reaction was quenched with saturated aqueous NH_4Cl , extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated. The residue was dissolved in methylene chloride (1 mL) and trifluoroacetic acid (1 mL) was added at ambient temperature. After 2 hours, the volatiles were removed under vacuum to afford the desired product (40 mg, 92%). LCMS calculated for $\text{C}_{27}\text{H}_{26}\text{N}_5\text{O}_6\text{S}$ (M+H)⁺: m/z=548.2. Found: 548.2.

Step 2. 2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-N,N-dimethylacetamide

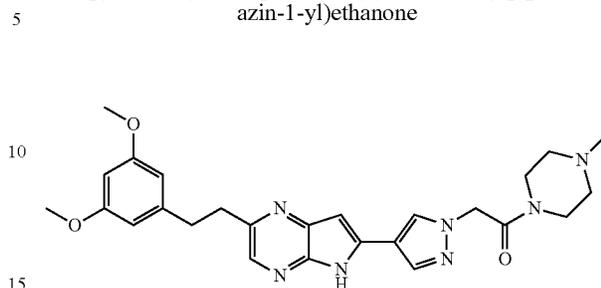


To a stirred solution of {4-[2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]-1H-pyrazol-1-yl}acetic acid (10.0 mg, 18.3 μ mol) in N,N-dimethylformamide (1.0 mL), N,N-dimethylamine (2.0 M in THF, 13.7 μ L, 27.4 μ mol), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (8.33 mg, 21.9 mmol) and N,N-diisopropylethylamine (12.7 μ L, 73.0 μ mol) were added sequentially at ambient temperature. After 1 hour, the reaction was quenched with saturated aqueous NH_4Cl , extracted with methylene chloride. The combined organic layers were dried over MgSO_4 , and then concentrated. The residue was dissolved in methanol (2.0 mL) and potassium carbonate (5.05 mg, 36.5 μ mol) was added. The reaction mixture was then warmed up to 60° C. After 2 hours, the crude mixture was cooled to ambient temperature and purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (2.8 mg) as its TFA salt. LCMS calculated for $\text{C}_{23}\text{H}_{27}\text{N}_6\text{O}_3$ (M+H)⁺: m/z=435.2. Found: 435.3.

58

Example 44

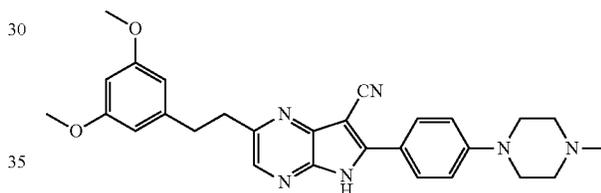
2-(4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)-1-(4-methylpiperazin-1-yl)ethanone



This compound was prepared using procedures analogous to those for Example 43, Step 2, with 1-methylpiperazine replacing N,N-dimethylamine (2.0 M in THF). LCMS calculated for $\text{C}_{26}\text{H}_{32}\text{N}_7\text{O}_3$ (M+H)⁺: m/z=490.3. Found: 490.3.

Example 45

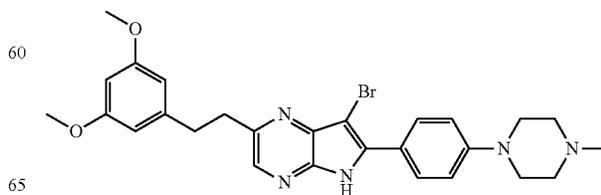
2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine-7-carbonitrile



To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine (from Example 1, Step 5, 50.0 mg, 10.9 μ mol) in N,N-dimethylformamide (2 mL), chlorosulfonyl isocyanate (24.0 μ L, 27.6 μ mol) was added at 0° C. The reaction mixture was then warmed to ambient temperature and kept stirring overnight. The volatiles were removed and the residue was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (1.2 mg) as its TFA salt. LCMS calculated for $\text{C}_{28}\text{H}_{31}\text{N}_6\text{O}_2$ (M+H)⁺: m/z=483.2. Found: 483.2.

Example 46

7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine

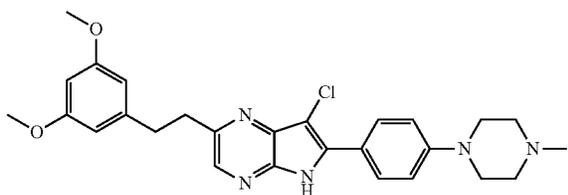


59

To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine (from Example 1, Step 5, 120 mg, 0.262 mmol) in methylene chloride (2 mL), a solution of N-bromosuccinimide (46.7 mg, 0.262 mmol) in methylene chloride (1 mL) was added dropwise at 0° C. After 30 minutes, the reaction was quenched with saturated aqueous NaHCO₃, then extracted with methylene chloride. The combined organic layers were dried over MgSO₄, and then concentrated. The residue was purified on silica gel (eluting with 0 to 10% MeOH in dichloromethane (DCM)) to give the desired product (110 mg, 78%). LCMS calculated for C₂₇H₃₁BrN₅O₂ (M+H)⁺: m/z=536.2. Found: 536.2.

Example 47

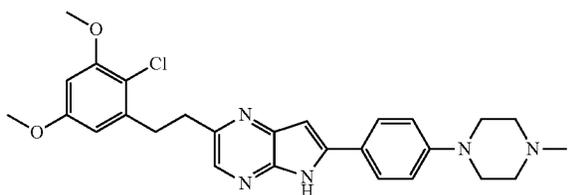
7-chloro-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



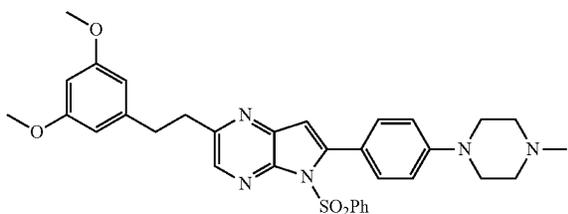
This compound was prepared using procedures analogous to those for Example 30, with N-chlorosuccinimide replacing N-bromosuccinimide. LCMS calculated for C₂₇H₃₁ClN₅O₂ (M+H)⁺: m/z=492.2. Found: 492.3.

Example 48

2-[2-(2-chloro-3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



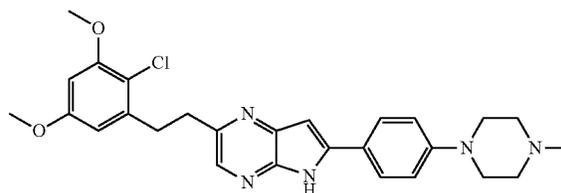
Step 1. 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



60

A stirred mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from Example 1, step 4, 30.0 mg, 59.7 μmol), 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (from Alfa Aesar, cat# H51659, 19.8 mg, 6.57 μmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (4.9 mg, 5.97 mmol), and potassium phosphate (25.4 mg, 119 μmol) in water (0.2 mL)/1,4-dioxane (1 mL) was heated at 88° C. After another 1 hour, the reaction mixture was quenched with saturated aq. NH₄Cl, extracted with methylene chloride. The combined organic layers were dried over MgSO₄, then concentrated to give the desired product (25 mg, 70%). LCMS calculated for C₃₃H₃₆N₅O₄S (M+H)⁺: m/z=598.3. Found: 598.3.

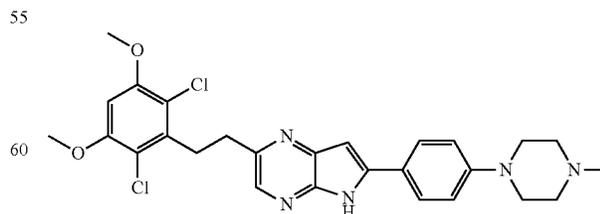
Step 2. 2-[2-(2-chloro-3,5-dimethoxyphenyl)ethyl]-6,4-(4-methylpiperazin-1-yl)phenyl 1-5H-pyrrolo[2,3-b]pyrazine



To a stirred solution of 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (25 mg, 41.9 μmol) in methylene chloride (2 mL) at 0° C., a solution of sulfonyl chloride (6.0 μL, 75 μmol) in methylene chloride (1 mL) was added dropwise. After 30 minutes, the volatiles were removed and the residue was dissolved in methanol (2 mL) and potassium carbonate (27.5 mg, 0.199 mmol) was added. The reaction mixture was then warmed up to 60° C. After 30 minutes, the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (2.5 mg) as its TFA salt. LCMS calculated for C₂₇H₃₁ClN₅O₂ (M+H)⁺: m/z=492.2. Found: 492.2.

Example 49

2-[2-(2,6-dichloro-3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine

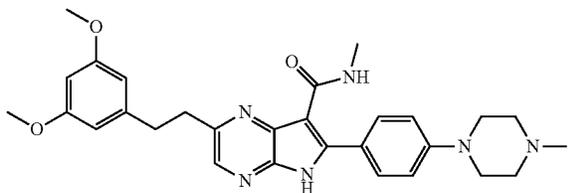


This compound was prepared using procedures same with those for Example 48. LCMS calculated for C₂₇H₃₀Cl₂N₅O₂ (M+H)⁺: m/z=526.2. Found: 526.2.

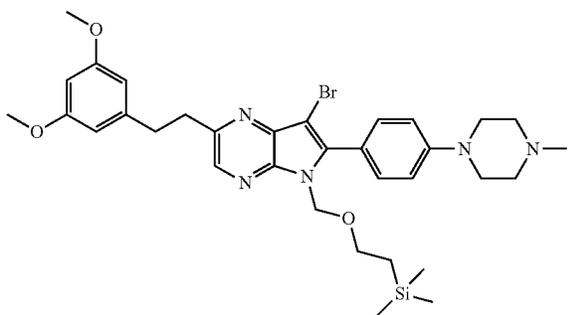
61

Example 50

2-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide

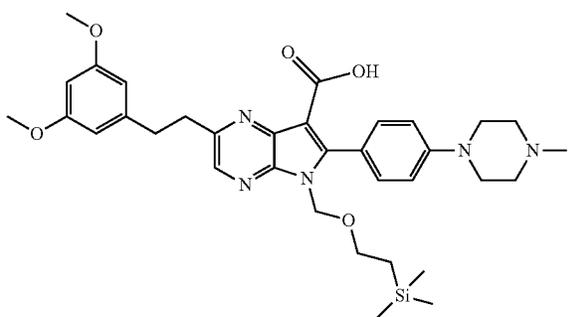


Step 1. 7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine



To a stirred solution of 7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine (from Example 46, 110 mg, 0.205 mmol) in tetrahydrofuran (2 mL), sodium hydride (12.0 mg, 0.300 mmol) was added at 0° C. After 10 min, [β-(trimethylsilyl)ethoxy]methyl chloride (55.7 μL, 0.315 mmol) was added dropwise. After another 1 hour, the reaction was quenched with saturated aqueous NH₄Cl, extracted with methylene chloride. The combined organic layers were dried over MgSO₄, and then concentrated. The residue was purified on silica gel (eluting with 0 to 8% MeOH in DCM) to give the desired product (55 mg, 31%). LCMS calculated for C₃₃H₄₅BrN₅O₃Si (M+H)⁺: m/z=666.2. Found: 666.3.

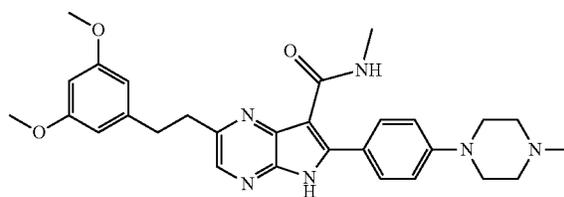
Step 2. 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid



62

The a stirred solution of 7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine (55 mg, 82.7 μmol) in tetrahydrofuran (2 mL), n-butyllithium (2.5 M in hexanes, 50 μL, 0.125 mmol) was added at 78° C. After 10 minutes, dry CO₂ (prepared by passing the CO₂ through drying tube) was bubbled into the reaction. After 20 minutes, the reaction was quenched with saturated aqueous NH₄Cl, then extracted with methylene chloride. The combined organic layers were dried over MgSO₄, then concentrated to give the crude product (50 mg), which was used directly in the next step. LCMS calculated for C₃₄H₄₆BN₅O₅Si (M+H)⁺: m/z=632.3. Found: 632.3.

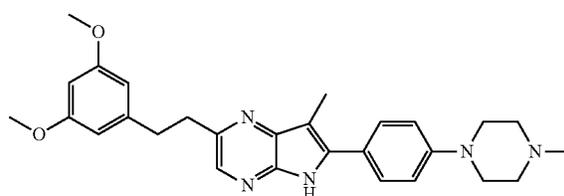
Step 3. 2-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide



To a stirred solution of crude 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-5H-pyrrolo[2,3-b]pyrazine-7-carboxylic acid (20 mg, 31.6 μmol) in N,N-dimethylformamide (2 mL), HATU (12.0 mg, 31.6 μmol), 2.0 M methylamine in THF (15.8 μL, 31.6 μmol) and N,N-diisopropylamine (11.0 μL, 63.3 mmol) were added sequentially at ambient temperature. After 1 hour, the reaction was quenched with saturated aqueous NH₄Cl, extracted with methylene chloride. The combined organic layers were dried over MgSO₄, concentrated. The residue was dissolved in methylene chloride (1 mL) and trifluoroacetic acid (1 mL) was added at ambient temperature. After 2 hours, the volatiles were removed under vacuum and the residue was dissolved in methanol (1 mL), followed by the addition of ethylenediamine (0.1 mL). After another 1 hour, the reaction mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.5 mg) as its TFA salt. LCMS calculated for C₂₉H₃₅N₆O₃ (M+H)⁺: m/z=515.3. Found: 515.2.

Example 51

2-[2-(3,5-dimethoxyphenyl)ethyl]-7-methyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine

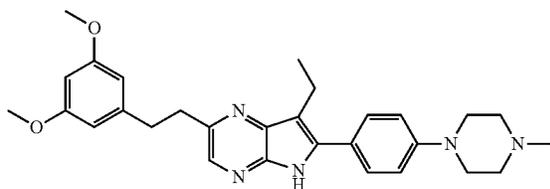


63

To a stirred solution of 7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine (from Example 46, 20.0 mg, 37.3 μmol) and Pd(dppf)Cl₂ (2.7 mg, 3.7 μmol) in 1,4-dioxane (0.8 mL), dimethylzinc (2.0 M in toluene, 47 μL , 94.0 μmol) was added at ambient temperature. The reaction mixture was then warmed up to 90° C. After 4 hours, the volatiles were removed and the residue was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (4.2 mg) as its TFA salt. LCMS calculated for C₂₈H₃₄N₅O₂ (M+H)⁺: m/z=472.2. Found: 472.2.

Example 52

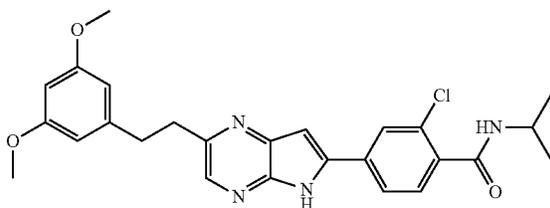
2-[2-(3,5-dimethoxyphenyl)ethyl]-7-ethyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine



A stirred mixture of 7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine (from Example 46, 10.0 mg, 18.6 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (1.22 mg, 1.49 μmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.53 μL , 14.9 μmol), and potassium phosphate (6.33 mg, 29.8 μmol) in water (0.2 mL)/1,4-dioxane (0.5 mL) was heated at 88° C. After 1 hour, the volatiles were removed and the residue was dissolved in methanol (1 mL). Pd/C (10% w/w, 1.59 mg, 1.49 μmol) was then added. The reaction mixture was stirred under H₂ at ambient temperature. After 2 hours, the crude mixture was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (3.2 mg) as its TFA salt. LCMS calculated for C₂₉H₃₆N₅O₂ (M+H)⁺: m/z=486.2. Found: 486.2; ¹H NMR (400 MHz, DMSO-d₆): δ 11.76 (s, 1H), 9.68 (s, 1H), 8.03 (s, 1H), 7.61 (d, J=9.0 Hz, 2H), 7.16 (d, J=9.0 Hz, 2H), 6.39 (d, J=2.4 Hz, 2H), 6.28 (t, J=2.0 Hz, 1H), 3.99 (d, J=11.5 Hz, 2H), 3.68 (s, 6H), 3.53 (d, J=12.0 Hz, 2H), 3.20-2.97 (m, 8H), 2.91 (q, J=7.5 Hz, 2H), 2.87 (s, 3H), 1.28 (t, J=7.5 Hz, 3H) ppm.

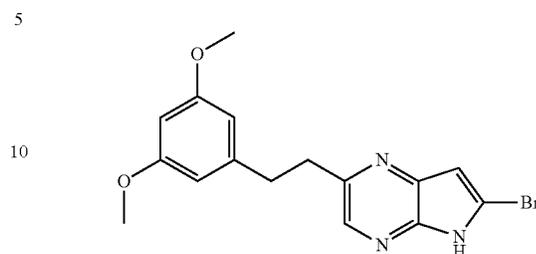
Example 53

2-Chloro-4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N-isopropylbenzamide



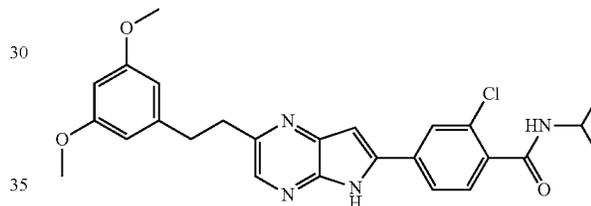
64

Step 1. 6-Bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine



6.0 M Potassium hydroxide in water (0.50 mL, 3.0 mmol) was added to a solution of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (0.5 g, 0.9952 mmol) (from Example 1, Step 4) in THF (10 mL) and then the mixture was stirred at 70° C. for 3 hours. Most of the solvent was removed and the residue was treated with saturated ammonium chloride. The formed precipitate was filtered, washed with water, and dried to provide the desired product (0.34 g, 94%). LCMS calculated for C₁₆H₁₇BrN₃O (M+H)⁺: m/z=362.0. Found 362.0.

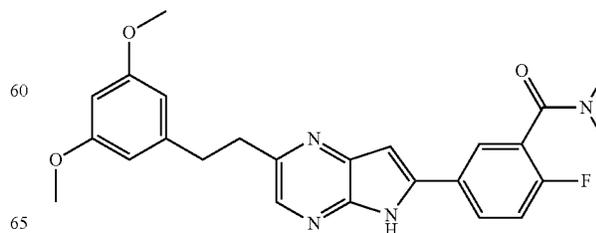
Step 2. 2-Chloro-4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N-isopropylbenzamide



A mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine (10.0 mg, 0.0276 mmol), 2-chloro-N-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (13.0 mg, 0.041 mmol, from Combi-Blocks), sodium carbonate (5.8 mg, 0.055 mmol) and dichloro(bis{di-tert-butyl[4-(dimethylamino)phenyl]phosphoranyl})-palladium (0.59 mg, 0.00083 mmol) in 1,4-dioxane (0.5 mL)/water (0.1 mL) was evacuated and refilled with N₂ three times. The reaction was then stirred at 110° C. overnight. The mixture was purified by RP-HPLC (pH=2, TFA as the media) to afford the desired product as TFA salt. LCMS calculated for C₂₆H₂₈ClN₄O₃ (M+H)⁺: m/z=479.2. Found 479.1.

Example 54

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-fluoro-N,N-dimethylbenzamide

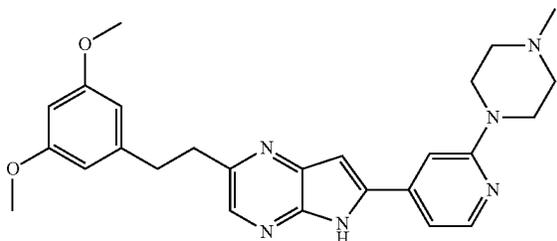


65

The compound was prepared by using procedure analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 3-(dimethylcarbamoyl)-4-fluorophenylboronic acid (from Combi-Blocks). LCMS calculated for $C_{25}H_{26}FN_4O_3$ (M+H)⁺: m/z=449.2. Found 449.1.

Example 55

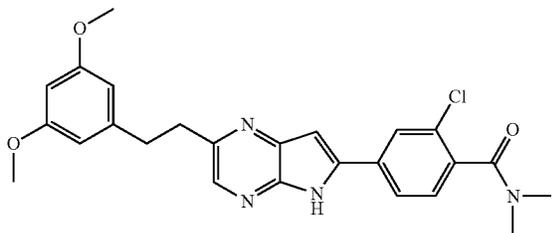
2-(3,5-Dimethoxyphenethyl)-6-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine



The compound was prepared by using procedure analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine (from Boron Molecular). LCMS calculated for $C_{26}H_{31}N_6O_2$ (M+H)⁺: m/z=459.2. Found 459.1.

Example 56

2-Chloro-4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N,N-dimethylbenzamide

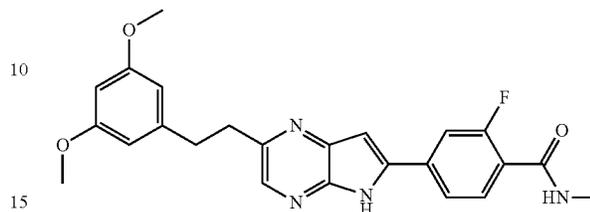


The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 3-chloro-4-(dimethylcarbamoyl)phenylboronic acid (from Combi-Blocks). LCMS calculated for $C_{25}H_{26}ClN_4O_3$ (M+H)⁺: m/z=465.2. Found 465.1.

66

Example 57

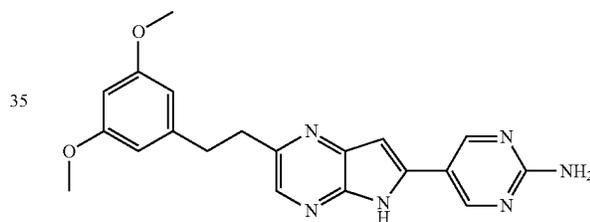
4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-fluoro-N-methylbenzamide



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 3-fluoro-4-(methylcarbamoyl)phenylboronic acid (from Combi-Blocks). LCMS calculated for $C_{24}H_{24}FN_4O_3$ (M+H)⁺: m/z=435.2. Found 435.2.

Example 58

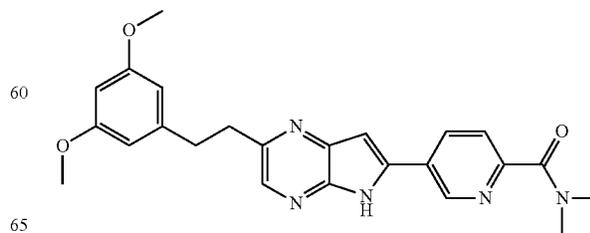
5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyrimidin-2-amine



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (from Boron Molecular). LCMS calculated for $C_{20}H_{11}N_6O_2$ (M+H)⁺: m/z=377.2. Found 377.1.

Example 59

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N,N-dimethylpicolinamide

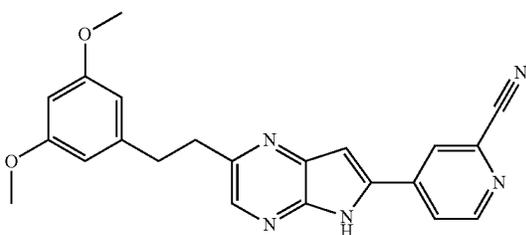


67

The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and N,N-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carboxamide (from PepTech Corp. Encyclopedia of Amino Acid Analogs and Boronic Acids). LCMS calculated for $C_{24}H_{26}N_5O_3$ (M+H)⁺: m/z=432.2. Found 432.1.

Example 60

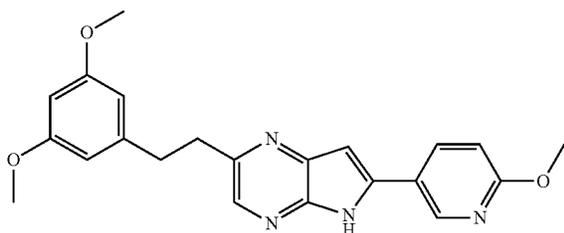
4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)picolinonitrile



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile (from CombiBlocks). LCMS calculated for $C_{22}H_{20}N_5O_2$ (M+H)⁺: m/z=386.2. Found 386.2.

Example 61

2-(3,5-Dimethoxyphenethyl)-6-(6-methoxypyridin-3-yl)-5H-pyrrolo[2,3-b]pyrazine

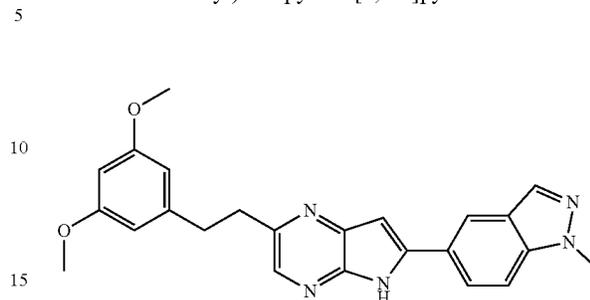


The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and (6-methoxypyridin-3-yl)boronic acid (from Aldrich). LCMS calculated for $C_{22}H_{23}N_4O_3$ (M+H)⁺: m/z=391.2. Found: m/z=391.1.

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Example 62

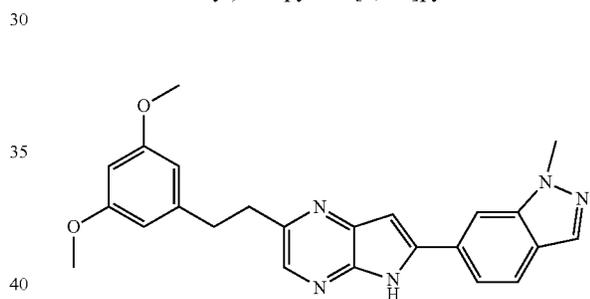
2-(3,5-Dimethoxyphenethyl)-6-(1-methyl-1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazine



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (from CombiBlocks). LCMS calculated for $C_{24}H_{24}N_5O_2$ (M+H)⁺: m/z=414.2. Found 414.2.

Example 63

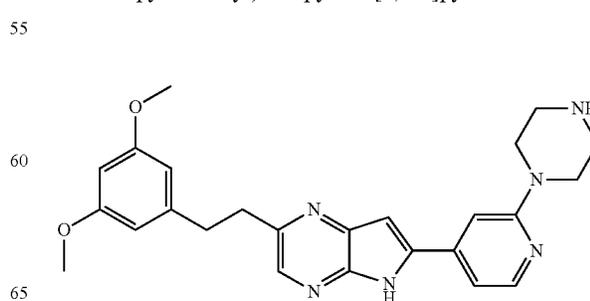
2-(3,5-Dimethoxyphenethyl)-6-(1-methyl-1H-indazol-6-yl)-5H-pyrrolo[2,3-b]pyrazine



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (from CombiBlocks). LCMS calculated for $C_{24}H_{24}N_5O_2$ (M+H)⁺: m/z=414.2. Found 414.2.

Example 64

2-(3,5-Dimethoxyphenethyl)-6-(2-(piperazin-1-yl)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine



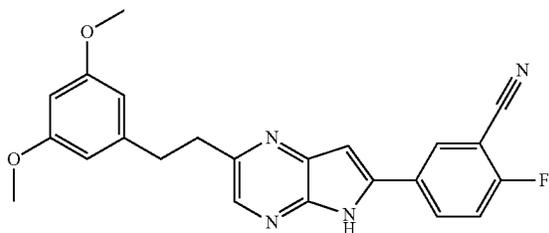
65

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The compound was prepared by using procedure analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine (from Aldrich). LCMS calculated for $C_{25}H_{29}N_6O_2$ (M+H)⁺: $m/z=445.2$. Found 445.2.

Example 65

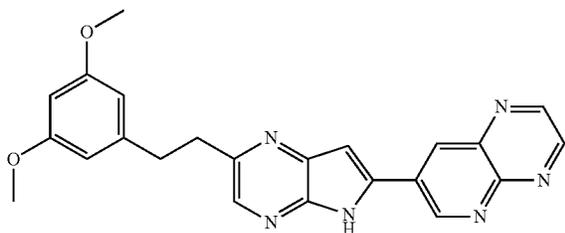
5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-fluorobenzonitrile



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and (4-cyano-3-fluorophenyl)boronic acid (from Aldrich). LCMS calculated for $C_{23}H_{20}FN_4O_2$ (M+H)⁺: $m/z=403.2$. Found 403.2.

Example 66

7-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyrido[2,3-b]pyrazine

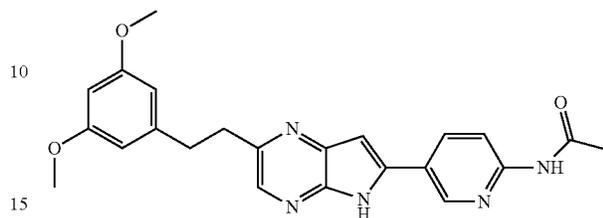


The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrido[2,3-b]pyrazine (from Combi-Blocks). LCMS calculated for $C_{23}H_{21}N_6O_2$ (M+H)⁺: $m/z=413.2$. Found 413.2.

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Example 67

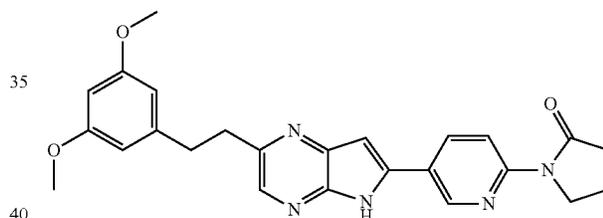
N-(5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-2-yl)acetamide



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]acetamide (from Combi-Blocks). LCMS calculated for $C_{23}H_{24}N_5O_3$ (M+H)⁺: $m/z=418.2$. Found 418.1.

Example 68

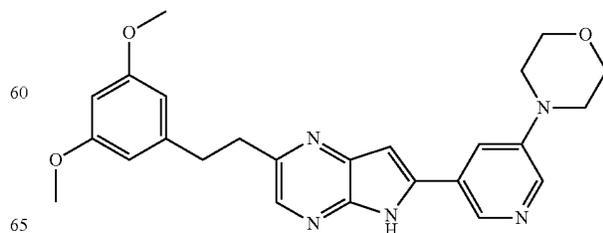
1-(5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-2-yl)pyrrolidin-2-one



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]pyrrolidin-2-one (from JPM2 Pharmaceuticals). LCMS calculated for $C_{25}H_{26}N_5O_3$ (M+H)⁺: $m/z=444.2$. Found 444.2.

Example 69

4-(5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-3-yl)morpholine

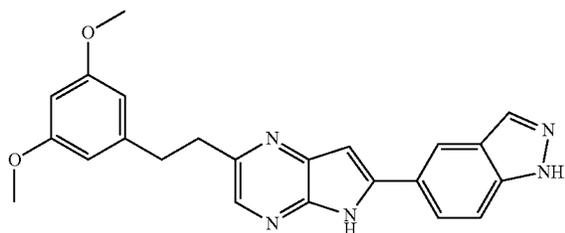


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The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl]morpholine (from Small Molecules). LCMS calculated for $C_{25}H_{28}N_5O_3$ (M+H)⁺: m/z=446.2. Found 446.1.

Example 70

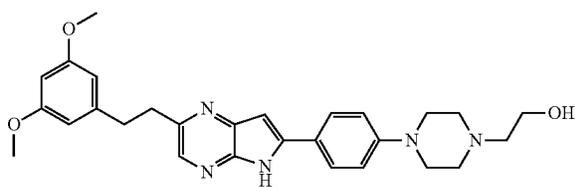
2-(3,5-Dimethoxyphenethyl)-6-(1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazine



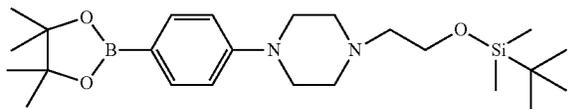
The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazine (from Combi-Blocks). LCMS calculated for $C_{23}H_{22}N_5O_2$ (M+H)⁺: m/z=400.2. Found 400.1.

Example 71

2-(4-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)piperazin-1-yl)ethanol



Step 1. 1-(2-[[t-Butyl(dimethyl)silyl]oxy]ethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine

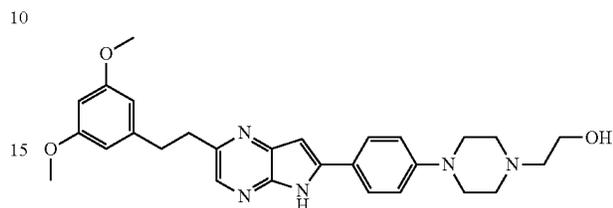


A mixture of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (0.1 g, 0.5 mmol, from Boron Molecular), (2-bromoethoxy)(tert-butyl)dimethylsilane (0.18 g, 0.75 mmol) and cesium carbonate (0.32 g, 1.0 mmol) in acetonitrile (2.0 mL) was stirred at 40° C. overnight. The residue was purified by flash chromatography on a silica gel

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column with ethyl acetate in hexanes (0-30%) to afford the desired product (0.2 g, 88%). LCMS calculated for $C_{24}H_{44}BN_2O_3Si$ (M+H)⁺: m/z=447.3. Found 447.3.

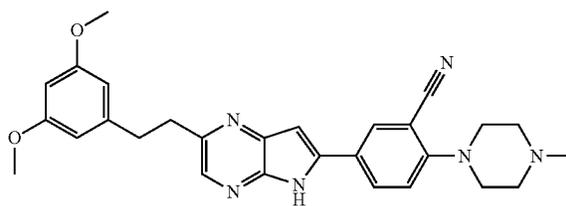
Step 2. 2-(4-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)piperazin-1-yl)ethanol



A mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine (10.0 mg, 0.0276 mmol), 1-(2-[[t-butyl(dimethyl)silyl]oxy]ethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (18.0 mg, 0.041 mmol), sodium carbonate (5.8 mg, 0.055 mmol), and dichloro(bis{di-tert-butyl[4-(dimethylamino)phenyl]phosphoranyl})-palladium (0.59 mg, 0.00083 mmol) in 1,4-dioxane (0.5 mL)/water (0.1 mL) was evacuated and refilled with N₂ three times. The reaction was then stirred at 110° C. overnight. The mixture was filtered and then to the filtrate was added conc. HCl (0.05 mL) and then the reaction was stirred at room temperature for 2 hours. The mixture was purified by RP-HPLC (pH=2, TFA as the media) to afford the desired product as TFA salt. LCMS calculated for $C_{28}H_{34}N_5O_3$ (M+H)⁺: m/z=488.3. Found 488.2.

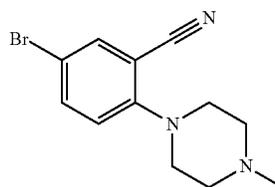
Example 72

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-(4-methylpiperazin-1-yl)benzonitrile



Step 1.

5-Bromo-2-(4-methylpiperazin-1-yl)benzonitrile

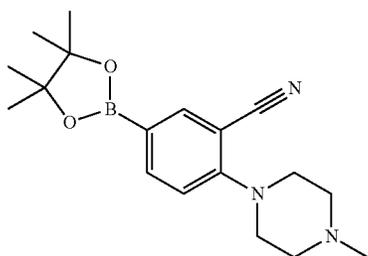


A mixture of 5-bromo-2-fluorobenzonitrile (0.20 g, 1.0 mmol), 1-methylpiperazine (0.15 g, 1.5 mmol) and triethyl-

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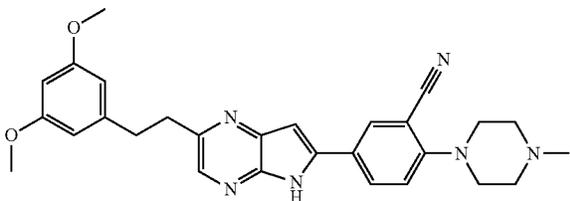
amine (0.20 g, 2.0 mmol) in 1-butanol (3.0 mL) was heated at 140° C. for 2 hours. The solvent was removed under reduced pressure and the residue was diluted with ethyl acetate, washed with water, brine, dried over Na₂SO₄, filtered and concentrated to provide the desired product (0.26 g, 92%). LCMS calculated for C₁₂H₁₅BrN₃(M+H)⁺: m/z=280.0. Found 280.0.

Step 2. 2-(4-Methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotrile



A mixture of 5-bromo-2-(4-methylpiperazin-1-yl)benzotrile (0.28 g, 1.0 mmol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (0.38 g, 1.5 mmol), potassium acetate (0.29 g, 3.0 mmol), and the [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (0.041 g, 0.050 mmol) in 1,4-dioxane (5.0 mL) was degassed with nitrogen and then the reaction was stirred at 100° C. overnight. The mixture was filtered through silica gel and washed with methanol. The solvent was concentrated. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0-8%) to afford the desired product (0.2 g, 88%). LCMS calculated for C₁₈H₂₇BN₃O₂(M+H)⁺: m/z=328.2. Found 328.1.

Step 3. 5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-(4-methylpiperazin-1-yl)benzotrile

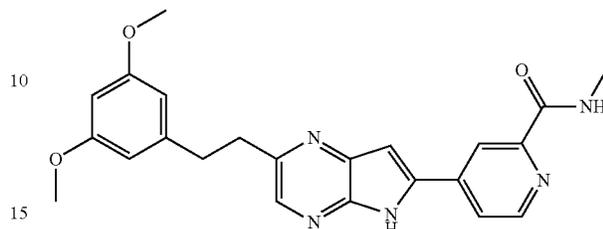


The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 2-(4-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotrile. LCMS calculated for C₂₈H₃₁N₆O₂(M+H)⁺: m/z=483.2. Found 483.3.

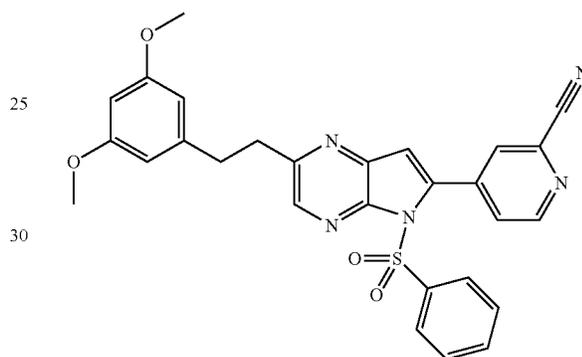
74

Example 73

4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N-methylpicolinamide

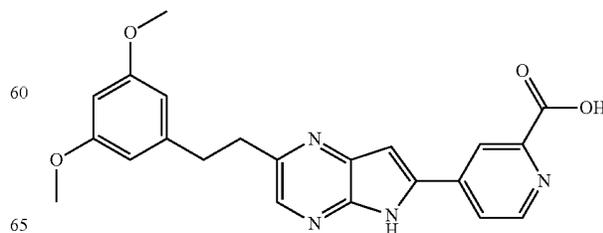


Step 1. 4-(2-(3,5-Dimethoxyphenethyl)-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)picolinonitrile



A mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (60.0 mg, 0.119 mmol) (from Example 1, Step 4), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-carbonitrile (0.041 g, 0.18 mmol from Combi-Blocks), sodium carbonate (25 mg, 0.24 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (20. mg, 0.024 mmol) in acetonitrile (1 mL)/water (0.2 mL) was evacuated and the refilled with N₂ and then stirred at 100° C. for 3 hours. The mixture was diluted with ethyl acetate, washed with saturated NaHCO₃, water, brine, then dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in methylene chloride (0-60%) to afford the desired product (0.055 g, 85%). LCMS calculated for C₂₈H₂₄N₅O₄S (M+H)⁺: m/z=526.2. Found 526.2.

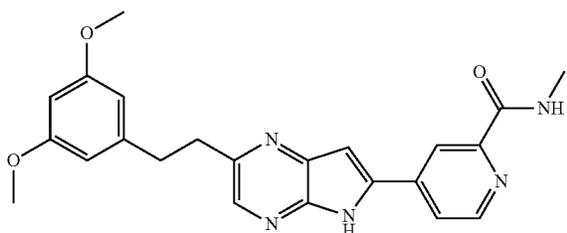
Step 2. 4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)picolinic acid



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6.0 M Potassium hydroxide in water (0.2 mL, 1 mmol) was added to a solution of 4-[2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]pyridine-2-carbonitrile (50.0 mg, 0.0951 mmol) in THF (0.5 mL) and then the reaction was stirred at 90° C. for 5 hours. The mixture was then acidified to pH=2 by adding conc. HCl and then the solvent was removed to provide the desired crude product which was used in the next step directly. LCMS calculated for $C_{22}H_{21}N_4O_4(M+H)^+$: $m/z=405.2$. Found 405.2.

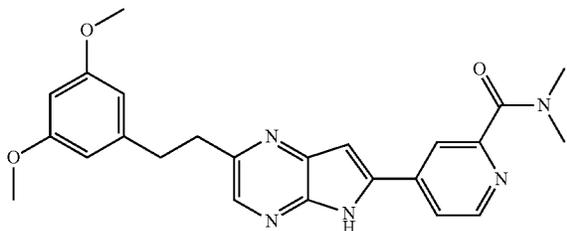
Step 3. 4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N-methylpicolinamide



2.0 M Methylamine in THF (0.1 mL, 0.3 mmol) was added to a solution of 4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}pyridine-2-carboxylic acid (6.10 mg, 0.0151 mmol) and benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (10 mg, 0.02 mmol) in dimethylformamide (DMF) (0.5 mL) at r.t followed by adding triethylamine (6.3 μ L, 0.045 mmol) and then the reaction was stirred at room temperature for 2 hours. The mixture was purified by RP-HPLC (pH=2, TFA as the media) to afford the desired product as TFA salt. LCMS calculated for $C_{23}H_{24}N_5O_3(M+H)^+$: $m/z=418.2$. Found 418.1.

Example 74

4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N,N-dimethylpicolinamide



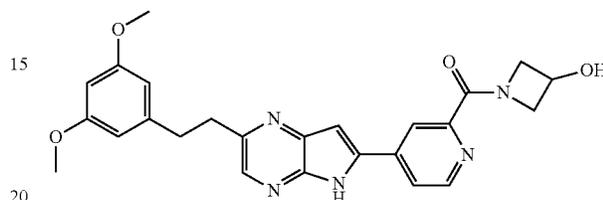
The compound was prepared by using procedures analogous to those described for the synthesis of Example 73, Step 3 starting from 4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}pyridine-2-carboxylic acid and

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N,N-dimethyl amine (2.0 M in THF). LCMS calculated for $C_{24}H_{26}N_5O_3(M+H)^+$: $m/z=432.2$. Found 432.2.

Example 75

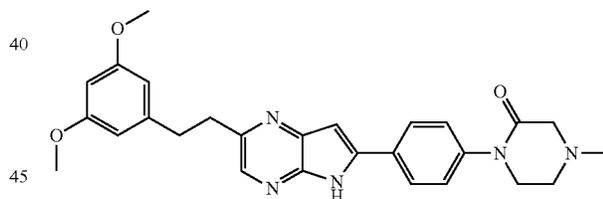
4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-2-yl(3-hydroxyazetid-1-yl)methanone



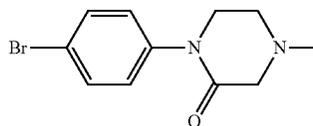
The compound was prepared by using procedure analogous to those described for the synthesis of Example 73, Step 3 starting from 4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}pyridine-2-carboxylic acid and 3-hydroxyazetidine hydrochloride (from Oakwood). LCMS calculated for $C_{25}H_{26}N_5O_4(M+H)^+$: $m/z=460.2$. Found 460.2.

Example 76

1-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)-4-methylpiperazin-2-one



Step 1. 1-(4-Bromophenyl)-4-methylpiperazin-2-one

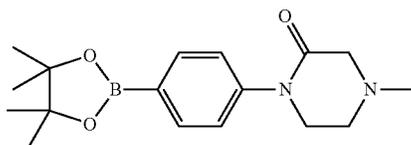


Sodium triacetoxyborohydride (0.25 g, 1.2 mmol) was added to a solution of 1-(4-bromophenyl)piperazin-2-one (200.0 mg, 0.7840 mmol, from J&W PharmLab product) and 11.0 M formaldehyde in water (0.21 mL, 2.4 mmol) in methylene chloride (3 mL, 50 mmol) and then the reaction was stirred at r.t for 1 hour. The mixture was diluted with methylene chloride, washed with saturated $NaHCO_3$, water, brine, then dried over Na_2SO_4 , filtered and concentrated to provide

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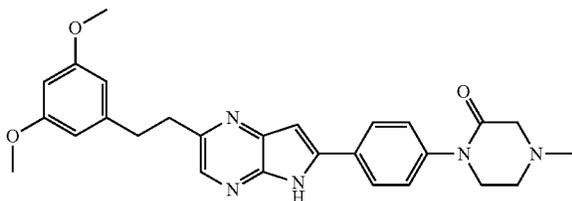
the product which was used in the next step. LCMS calculated for $C_{11}H_{14}BrN_2O$ (M+H)⁺: m/z=269.0. Found 269.0.

Step 2. 4-Methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-2-one



The compound was prepared by using procedure analogous to those described for the synthesis of Example 72, Step 2 starting from 1-(4-bromophenyl)-4-methylpiperazin-2-one. LCMS calculated for $C_{17}H_{26}BN_2O_3$ (M+H)⁺: m/z=317.2. Found 317.2.

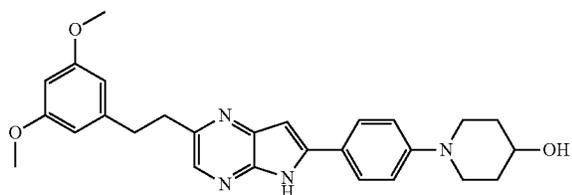
Step 3. 1-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)-4-methylpiperazin-2-one



A mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine (10.0 mg, 0.0276 mmol), 4-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazin-2-one (13 mg, 0.041 mmol), sodium carbonate (5.8 mg, 0.055 mmol) and dichloro(bis{di-tert-butyl[4-(dimethylamino)-phenyl]phosphoranyl})-palladium (0.59 mg, 0.00083 mmol) in 1,4-dioxane (0.5 mL)/water (0.1 mL) was evacuated and refilled with N_2 three times. The reaction was stirred at 110° C. overnight. The mixture was purified by RP-HPLC (pH=2, TFA as the media) to afford the desired product as TFA salt. LCMS calculated for $C_{27}H_{30}N_5O_3$ (M+H)⁺: m/z=472.2. Found 472.2.

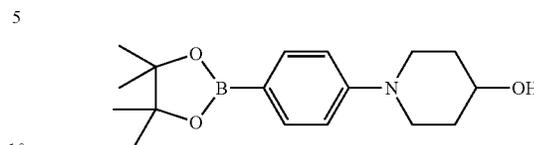
Example 77

1-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)piperidin-4-ol



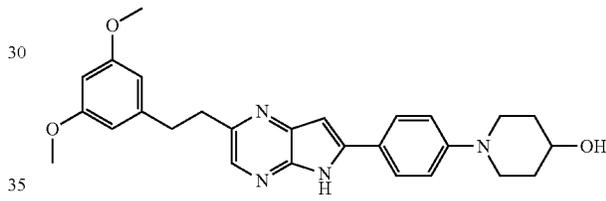
78

Step 1. 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol



Sodium tetrahydroborate (0.012 g, 0.33 mmol) was added to a mixture of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidin-4-one (0.050 g, 0.17 mmol, from Combi-Blocks) in methanol (1.0 mL) at 0° C. and then the reaction was stirred at 0° C. for 1 hour. The solvent was removed and the residue was treated with water and then filtered. The residue was dried to provide the desired product as a white solid. LCMS calculated for $C_{17}H_{27}BNO_3$ (M+H)⁺: m/z=304.2. Found 304.1.

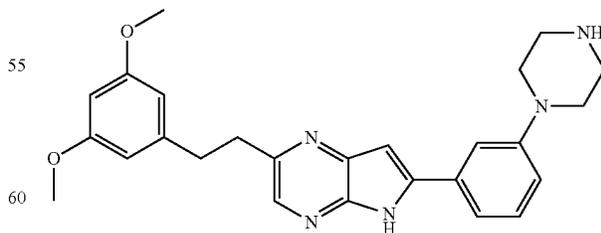
Step 2. 1-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)piperidin-4-ol



The compound was prepared by using procedure analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol. LCMS calculated for $C_{27}H_{31}N_4O_3$ (M+H)⁺: m/z=459.2. Found 459.3.

Example 78

2-(3,5-Dimethoxyphenethyl)-6-(3-(piperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine



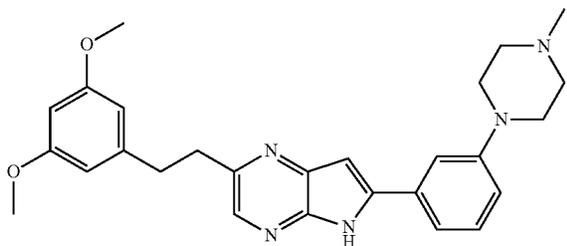
The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-[3-(4,4,5,5-tetramethyl-1,

79

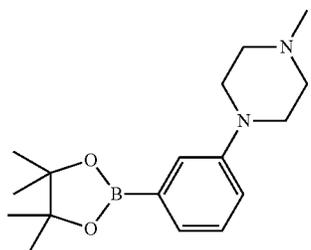
3,2-dioxaborolan-2-yl)phenyl]piperazine. LCMS calculated for $C_{26}H_{30}N_5O_2(M+H)^+$: $m/z=444.2$. Found 444.2.

Example 79

2-(3,5-Dimethoxyphenethyl)-6-(3-(4-methylpiperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine

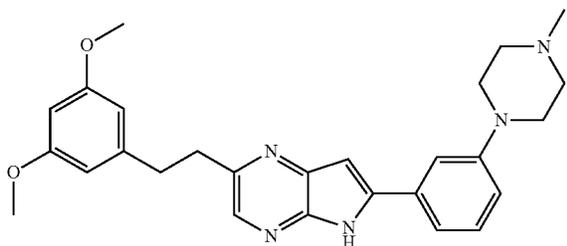


Step 1. 1-Methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine



Sodium triacetoxyborohydride (0.066 g, 0.31 mmol) was added to a solution of 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (60.0 mg, 0.208 mmol, from Boron Molecular) and 11.0 M aqueous formaldehyde (0.057 mL, 0.62 mmol) in methylene chloride (0.8 mL, 10 mmol) and then the reaction was stirred at r.t. for 1 hour. The mixture was diluted with methylene chloride, washed with saturated $NaHCO_3$, water, brine, then dried over Na_2SO_4 , filtered and concentrated to provide the product which was used in the next step. LCMS calculated for $C_{17}H_{28}BN_2O_2(M+H)^+$: $m/z=303.2$. Found 303.2.

Step 2. 2-(3,5-Dimethoxyphenethyl)-6-(3-(4-methylpiperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine



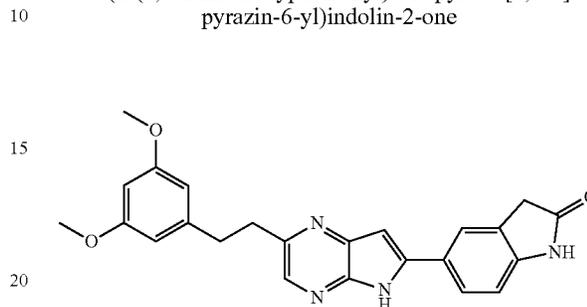
The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step

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2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-methyl-4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine. LCMS calculated for $C_{27}H_{32}N_5O_3(M+H)^+$: $m/z=458.3$. Found 458.3.

Example 80

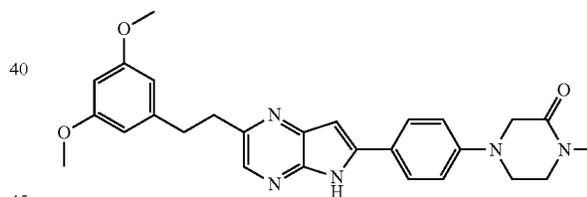
5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)indolin-2-one



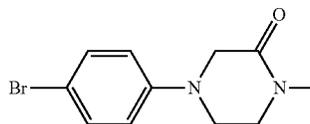
The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (from Combi-Blocks). LCMS calculated for $C_{24}H_{23}N_4O_3(M+H)^+$: $m/z=415.2$. Found 415.3.

Example 81

4-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)-1-methylpiperazin-2-one



Step 1. 4-(4-Bromophenyl)-1-methylpiperazin-2-one

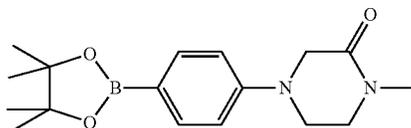


A mixture of 1,4-dibromobenzene (470 mg, 2.0 mmol), 1-methylpiperazin-2-one hydrochloride (150 mg, 1.0 mmol, from J&W PharmLab), palladium acetate (6.7 mg, 0.030 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (0.035 g, 0.060 mmol), and cesium carbonate (0.98 g, 3.0 mmol) in toluene (5.0 mL) was evacuated and refilled with nitrogen three times and then the reaction was stirred at $105^\circ C$. overnight. The mixture was diluted with ethyl acetate, washed with water, brine, then dried over Na_2SO_4 , filtered and concentrated. The residue was purified

81

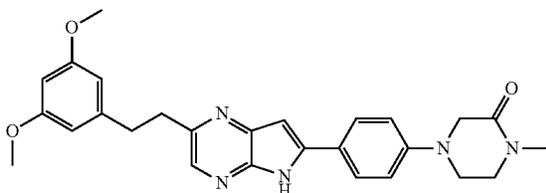
by flash chromatography on a silica gel column with ethyl acetate in hexane (0-60%) to afford the desired product (0.26 g, 49%). LCMS calculated for $C_{11}H_{14}BrN_2O$ ($M+H$)⁺: $m/z=269.0$. Found 269.0.

Step 2. 1-Methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-2-one



The compound was prepared by using procedures analogous to those described for the synthesis of Example 72, Step 2 starting from 4-(4-bromophenyl)-1-methylpiperazin-2-one. LCMS calculated for $C_{17}H_{26}BN_2O_3$ ($M+H$)⁺: $m/z=317.2$. Found 317.1.

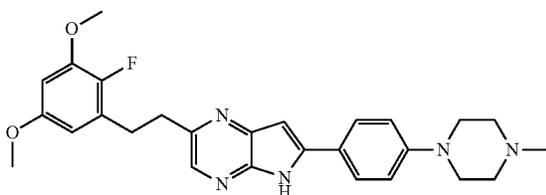
Step 3. 4-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)-1-methylpiperazin-2-one



The compound was prepared by using procedures analogous to those described for the synthesis of Example 53, Step 2 starting from 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazine and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-2-one. LCMS calculated for $C_{27}H_{30}N_5O_3$ ($M+H$)⁺: $m/z=472.2$. Found 472.1.

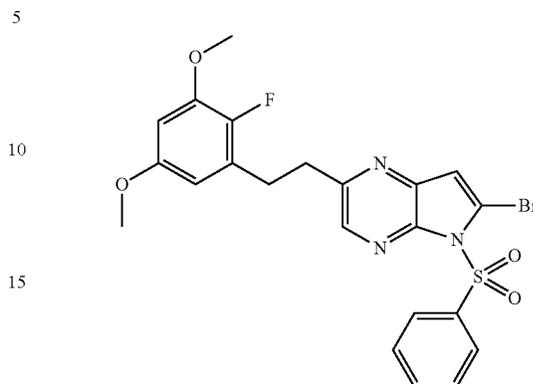
Example 82

2-(2-Fluoro-3,5-dimethoxyphenethyl)-6-(4-(4-methylpiperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine



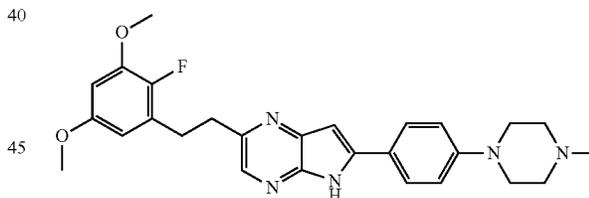
82

Step 1. 6-Bromo-2-(2-fluoro-3,5-dimethoxyphenethyl)-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



A mixture of 6-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (25.0 mg, 0.0498 mmol) and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (17.6 mg, 0.0498 mmol) in acetonitrile (0.3 mL)/water (0.06 mL) was stirred at 50° C. overnight. The solvent was removed and the residue was used in the next step w/o purification. LCMS calculated for $C_{22}H_{20}BrFN_3O_4S$ ($M+H$)⁺: $m/z=520.0$. Found 520.0.

Step 2. 2-[2-(2-Fluoro-3,5-dimethoxyphenethyl)-6-[4-(4-methylpiperazin-1-yl)phenyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine

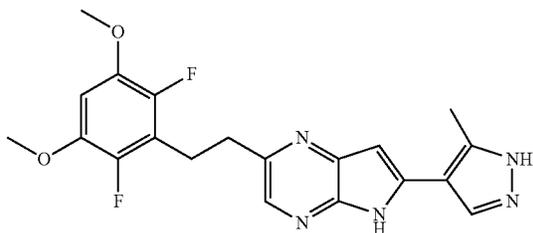


A mixture of 6-bromo-2-[2-(2-fluoro-3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (20.0 mg, 0.0384 mmol), 1-methyl-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine (17 mg, 0.058 mmol), sodium carbonate (8.1 mg, 0.077 mmol) in 1,4-dioxane (0.7 mL)/water (0.1 mL) was evacuated and refilled with N_2 three times. The reaction was stirred at 110° C. for 3 h and then filtered. The filtrate was concentrated, the residue was redissolved in THF (0.5 mL), and then 6.0 M KOH (0.1 mL) was added. The resulting mixture was stirred at 65° C. overnight and then purified by RP-HPLC (pH=2, TFA as the media) to afford the desired product as TFA salt. LCMS calculated for $C_{27}H_{31}FN_5O_2$ ($M+H$)⁺: $m/z=476.2$. Found 476.2.

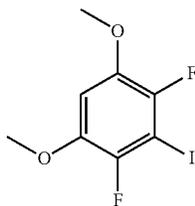
83

Example 83

2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-6-(5-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine

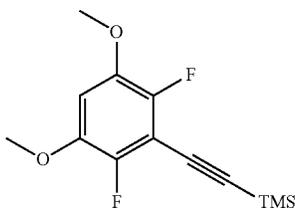


Step 1. 2,4-difluoro-3-iodo-1,5-dimethoxybenzene



To a stirred slurry of 2,6-difluoro-3,5-dimethoxyaniline (1.00 g, 5.29 mmol) in 6.0 M hydrogen chloride in water (9.00 mL, 54.0 mmol), a solution of sodium nitrite (0.383 g, 5.55 mmol) in water (2 mL) was added dropwise over 15 minutes at 0° C. After another 15 minutes, the resulting orange-red slurry was added to a solution of potassium iodide (3.50 g, 21.1 mmol) in water (5 mL) in small portions at 0° C. After addition, the reaction mixture was allowed to warm to room temperature and then it was stirred for 1 hour. Solid precipitated which was filtered out. The solid was washed with water and dried under vacuum to give the desired product (1.15 g, 70%). ¹H NMR (400 MHz, CDCl₃): δ 6.68 (t, J=8.0 Hz, 1H), 3.88 (s, 6H) ppm.

Step 2. [(2,6-difluoro-3,5-dimethoxyphenyl)ethynyl](trimethyl)silane



To a stirred mixture of 2,4-difluoro-3-iodo-1,5-dimethoxybenzene (740 mg, 2.47 mmol), (trimethylsilyl)acetylene (0.697 mL, 4.93 mmol), copper(I) iodide (38 mg, 0.20 mmol), and triethylamine (0.52 mL, 3.7 mmol) in N,N-dimethylformamide (DMF) (4 mL, 50 mmol), bis(triphenylphosphine) palladium(II) chloride (86 mg, 0.12 mmol) was added. The reaction mixture was stirred at room temperature for 70

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hours. The reaction was quenched with saturated aq. NH₄Cl, then extracted with methylene chloride. The combined organic layers were dried over MgSO₄, then concentrated. The residue was purified on silica gel (eluting with 0 to 30% EtOAc in hexanes) to give the desired product (630 mg, 94%).

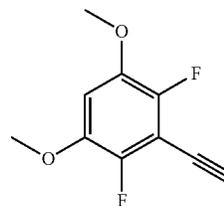
Step 3.

3-ethynyl-2,4-difluoro-1,5-dimethoxybenzene

10

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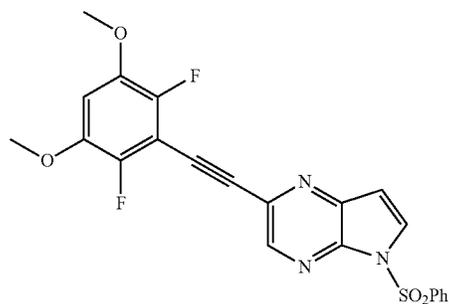
To a stirred solution of [(2,6-difluoro-3,5-dimethoxyphenyl)ethynyl](trimethyl)silane (630 mg, 2.33 mmol) in tetrahydrofuran (2 mL)/methanol (2 mL), cesium fluoride (354 mg, 2.33 mmol) was added at room temperature. After 1 hour, the reaction was quenched with saturated aq. NH₄Cl, then extracted with methylene chloride. The combined organic layers were dried over MgSO₄, concentrated to give the desired product (440 mg, 95%). ¹H NMR (300 MHz, CDCl₃): δ 6.62 (t, J=7.8 Hz, 1H), 3.89 (s, 7H) ppm.

Step 4. 2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethynyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine

40

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50



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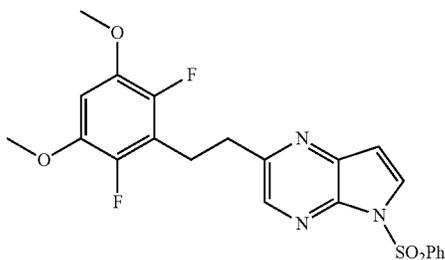
60

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To a stirred solution of 3-ethynyl-2,4-difluoro-1,5-dimethoxybenzene (340 mg, 1.72 mmol) and 2-bromo-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (696 mg, 2.06 mmol, from Example 1, Step 1) in N,N-dimethylformamide (4 mL), copper(I) iodide (26 mg, 0.14 mmol), bis(triphenylphosphine)palladium(II) chloride (60.0 mg, 0.0885 mmol) and triethylamine (0.36 mL, 2.6 mmol) were added sequentially at room temperature. After 14 hours, the reaction was quenched with saturated aq. NH₄Cl, then extracted with methylene chloride. The combined organic layers were dried over MgSO₄, then concentrated. The residue was purified on silica gel (eluting with 0 to 50% ethyl acetate (EtOAc) in hexanes) to give the desired product (490 mg, 63%). LCMS calculated for C₂₂H₁₅F₂N₃O₄S (M+H)⁺: m/z=456.1. Found: 456.1.

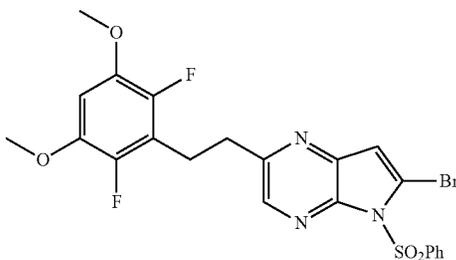
85

Step 5. 2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



To a stirred solution of 2-[(2,6-difluoro-3,5-dimethoxyphenyl)ethynyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (490 mg, 1.08 mmol) in tetrahydrofuran (8 mL)/methanol (10 mL), Pd/C (10% w/w, 365 mg, 0.343 mmol) was added. The resulting mixture was stirred under H₂ at ambient temperature. After 24 hr, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified on silica gel (eluting with 0 to 60% EtOAc in hexanes) to give the desired product (400 mg, 81%). LCMS calculated for C₂₂H₁₉F₂N₃O₄S (M+H)⁺: m/z=460.1. Found: 460.1.

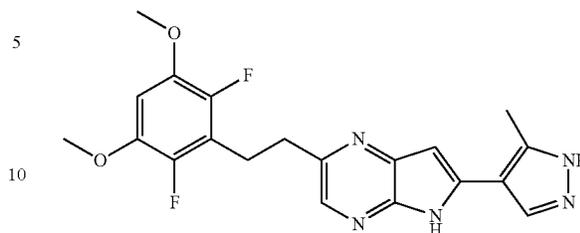
Step 6. 6-bromo-2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine



To a stirred solution of N,N-diisopropylamine (0.150 mL, 1.07 mmol) in tetrahydrofuran (0.48 mL) at 78° C., n-butyllithium (2.5 M in hexanes, 0.428 mL, 1.07 mmol) was added dropwise. After a white precipitate formed, the mixture was warmed up to 0° C. for 10 minutes. The resulting solution was added to a stirred solution of 2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (400 mg, 0.871 mmol) in tetrahydrofuran (3 mL) at 78° C. After 10 minutes, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (0.283 g, 0.870 mmol) in tetrahydrofuran (2 mL) was added dropwise. After another 1 hour, the reaction mixture was quenched with saturated aq. NH₄Cl, then extracted with methylene chloride. The combined organic layers were dried over MgSO₄, then concentrated. The residue was purified on silica gel (eluting with 0 to 50% EtOAc in hexanes) to give the desired product (330 g, 70%). LCMS calculated for C₂₂H₁₉BrF₂N₃O₄S (M+H)⁺: m/z=538.0. Found: 538.0.

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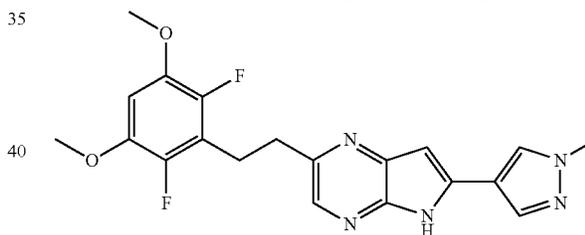
Step 7. 2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-6-(5-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine



A stirred mixture of 6-bromo-2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (15 mg, 28 μmol), (3-methyl-1H-pyrazol-4-yl)boronic acid (4.2 mg, 33 μmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complexed with dichloromethane (1:1) (1.8 mg, 2.2 μmol), and potassium phosphate (9.5 mg, 45 mmol) in water (0.2 mL)/1,4-dioxane (1 mL) was heated at 88° C. After 1 hour, the volatiles were removed under vacuum and the residue was dissolved in methanol (1 mL). Potassium carbonate (7.7 mg, 56 μmol) was added and the reaction mixture was warmed up to 60° C. After 0.5 hour, the reaction mixture was cooled to ambient temperature and was purified on RP-HPLC (XBridge C18 column, eluting with a gradient of acetonitrile/water containing 0.05% TFA, at flow rate of 30 mL/min) to give the desired product (5.1 mg, 46%) as its TFA salt. LCMS calculated for C₂₀H₂₀F₂N₅O₂ (M+H)⁺: m/z=400.2. Found: 400.2.

Example 84

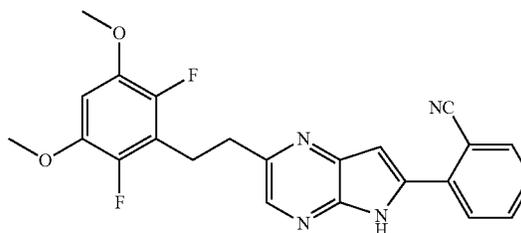
2-(2,6-difluoro-3,5-dimethoxyphenethyl)-6-(1-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 83, Step 7, with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole replacing (3-methyl-1H-pyrazol-4-yl)boronic acid. LCMS calculated for C₂₀H₂₀F₂N₅O₂ (M+H)⁺: m/z=400.2. Found: 400.1.

Example 85

2-(2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)benzonitrile

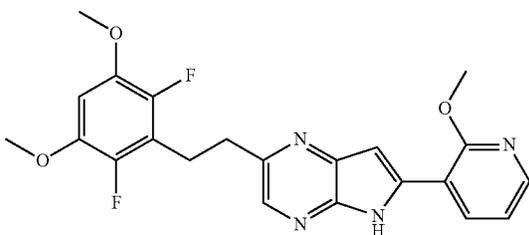


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This compound was prepared using procedures analogous to those for Example 83, Step 7, with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotrile replacing (3-methyl-1H-pyrazol-4-yl)boronic acid LCMS calculated for $C_{23}H_{19}F_2N_4O_2$ (M+H)⁺: m/z=421.1. Found: 421.1.

Example 86

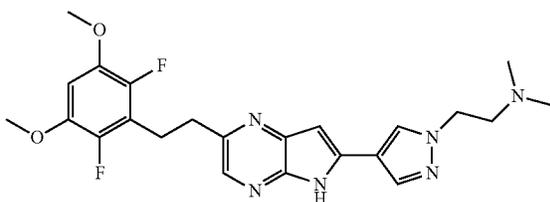
2-(2,6-difluoro-3,5-dimethoxyphenethyl)-6-(2-methoxy-pyridin-3-yl)-5H-pyrrolo[2,3-b]pyrazine



This compound was prepared using procedures analogous to those for Example 83, Step 7, with 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine replacing (3-methyl-1H-pyrazol-4-yl)boronic acid LCMS calculated for $C_{22}H_{21}F_2N_4O_3$ (M+H)⁺: m/z=427.2. Found: 427.2.

Example 87

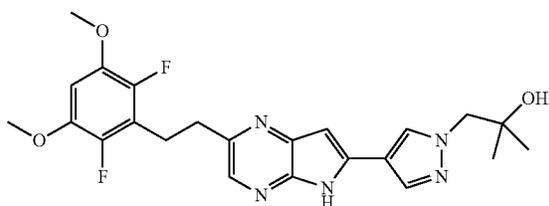
2-(4-(2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)-N,N-dimethylethanamine



This compound was prepared using procedures analogous to those for Example 83, Step 7, with N,N-dimethyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethanamine (from Example 34, Step 1) replacing (3-methyl-1H-pyrazol-4-yl)boronic acid LCMS calculated for $C_{23}H_{27}F_2N_6O_2$ (M+H)⁺: m/z=457.2. Found: 457.3.

Example 88

1-(4-(2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol

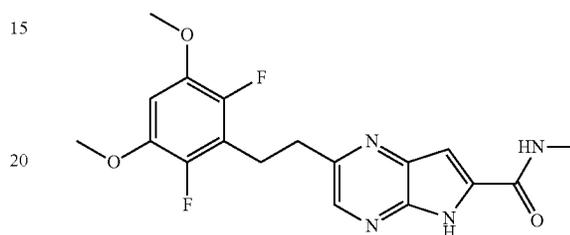


88

This compound was prepared using procedures analogous to those for Example 83, Step 7, with 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-ol (from Example 33, Step 1) replacing (3-methyl-1H-pyrazol-4-yl)boronic acid LCMS calculated for $C_{23}H_{26}F_2N_5O_3$ (M+H)⁺: m/z=458.2. Found: 458.2.

Example 89

2-(2,6-difluoro-3,5-dimethoxyphenethyl)-N-methyl-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide



This compound was prepared using procedures analogous to those for Example 25, with 2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine (from Example 83, Step 5) replacing 2-[2-(3,5-dimethoxyphenyl)ethyl]-5-(phenylsulfonyl)-5H-pyrrolo[2,3-b]pyrazine LCMS calculated for $C_{18}H_{19}F_2N_4O_3$ (M+H)⁺: m/z=377.2. Found: 377.2.

Example A

35 FGFR Enzymatic Assay

The inhibitor potency of compounds was measured in an enzyme assay that measures peptide phosphorylation using FRET measurements to detect product formation. Inhibitors were serially diluted in DMSO and a volume of 0.5 μ L was transferred to the wells of a 384-well plate. For FGFR3, a 10 μ L volume of FGFR3 enzyme (Millipore) diluted in assay buffer (50 mM HEPES, 10 mM $MgCl_2$, 1 mM EGTA, 0.01% Tween-20, 5 mM DTT, pH 7.5) was added to the plate and pre-incubated for 5-10 minutes. Appropriate controls (enzyme blank and enzyme with no inhibitor) were included on the plate. The assay was initiated by the addition of a 10 μ L solution containing biotinylated EQEDEPEGDYFEWLE peptide substrate (SEQ ID NO: 1) and ATP (final concentrations of 500 nM and 140 μ M respectively) in assay buffer to the wells. The plate was incubated at 25° C. for 1 hr. The reactions were ended with the addition of 10 μ L/well of quench solution (50 mM Tris, 150 mM NaCl, 0.5 mg/mL BSA, pH 7.8; added fresh 30 mM EDTA and Perkin Elmer Lance Reagents for HTRF at 3.75 nM Eu-antibody PY20 and 180 nM APC-Streptavidin). The plate was allowed to equilibrate for 1 hr before scanning the wells on a PheraStar plate reader.

FGFR1 and FGFR2 were measured under equivalent conditions with the following changes in enzyme and ATP concentrations: FGFR1, 0.02 nM and 210 μ M, respectively and FGFR2, 0.01 nM and 100 μ M, respectively.

GraphPad prism 3 was used to analyze the data. The IC_{50} values were derived by fitting the data to the equation for a sigmoidal dose-response with a variable slope. $Y = Bottom + (Top - Bottom) / (1 + 10^{((Log IC_{50} - X) * HillSlope)})$ where X is the logarithm of concentration and Y is the response.

The compounds of the invention were found to be inhibitors of one or more of FGFR1, FGFR2, and FGFR3 according to the above-described assay. IC₅₀ data is provided below in Table 1. The symbol “+” indicates an IC₅₀ less than 100 nM, the symbol “++” indicates an IC₅₀ of 100 to 500 nM, and the symbol “+++” indicates an IC₅₀ greater than 500 nM but less than 2700 nM. “N/P” means not provided.

TABLE 1

Example No.	FGFR1 IC ₅₀ (nM)	FGFR2 IC ₅₀ (nM)	FGFR3 IC ₅₀ (nM)
1	+	+	+
2	+	+	+
3	+	+	+
4	+	++	+++
5	+	+	+
6	+	+	++
7	+	+	++
8	+	++	++
9	+	++	+++
10	+	+	+++
11	+	+	+
12	+	+	+
13	+	+	+
14	+	+	++
15	+	+	+
16	+	+	++
17	+	+	++
18	+	+	+++
19	+	+	++
20	+	++	>1000
21	++	++	>2000
22	+	+	+
23	+	+	++
24	++	+++	>2000
25	++	++	>2000
26	+++	+++	>2000
27	+	++	>2000
28	++	+++	>2000
29	+	+	++
30	+	+	++
31	+	+	+
32	+	+	+
33	+	+	+
34	+	+	+
35	+	+	+
36	+	+	+
37	+	+	++
38	+	+	++
39	+	+	+
40	+	+	+
41	+	+	+
42	+	+	++
43	+	+	++
44	+	+	+
45	+	+	+
46	+	+	+
47	+	+	+
48	+	+	+
49	+	+	+
50	+	+	+++
51	+	+	+
52	+	+	+
53	+	+	+
54	+	+	++
55	+	+	++
56	+	+	+
57	+	+	+
58	+	+	++
59	+	+	++
60	+	+	++
61	+	+	++
62	+	+	+
63	+	+	++
64	+	+	+
65	+	+	N/P
66	+	+	>2000
67	+	+	++

TABLE 1-continued

Example No.	FGFR1 IC ₅₀ (nM)	FGFR2 IC ₅₀ (nM)	FGFR3 IC ₅₀ (nM)	
5	68	+	+	++
	69	+	+	++
	70	+	+	++
	71	+	+	+
	72	+	+	=
	73	+	+	+
10	74	+	+	++
	75	+	+	++
	76	+	+	+
	77	+	+	+
	78	+	+	+
	79	+	+	+
15	80	+	+	+
	81	+	+	+
	82	+	+	+
	83	+	+	+
	84	+	+	+
	85	+	+	+
20	86	+	+	+
	87	+	+	+
	88	+	+	+
	89	+	+	>400

Example B

FGFR3 Cell Proliferation/Survival Assays

A recombinant cell line over-expressing human FGFR3 was developed by stable transfection of the mouse pro-B Ba/F3 cells (obtained from the Deutsche Sammlung von Mikroorganismen and Zellkulturen) with a plasmid encoding the full length human FGFR3. Cells were sequentially selected for puromycin resistance and proliferation in the presence of heparin and FGF1. A single cell clone was isolated and characterized for functional expression of FGFR3. This Ba/F3-FGFR3 clone is used in cell proliferation assays, and compounds are screened for their ability to inhibit cell proliferation/survival. The Ba/F3-FGFR3 cells are seeded into 96 well, black cell culture plates at 3500 cells/well in RPMI1640 media containing 2% FBS, 20 ug/mL Heparin and 5 ng/mL FGF1. The cells were treated with 10 μ L of 10 \times concentrations of serially diluted compounds (diluted with medium lacking serum from 5 mM DMSO dots) to a final volume of 100 μ L/well. After 72 hour incubation, 100 μ L of Cell Titer Glo[®] reagent (Promega Corporation) that measures cellular ATP levels is added to each well. After 20 minute incubation with shaking, the luminescence is read on a plate reader. The luminescent readings are converted to percent inhibition relative to DMSO treated control wells, and the IC₅₀ values are calculated using GraphPad Prism software. Compounds having an IC₅₀ of 10 μ M or less are considered active. Other non-recombinant cancer cell lines representing a variety of tumor types including KMS-11 (multiple myeloma), RT112 (bladder cancer), KatoIII (gastric cancer), and H-1581 (lung) are used in similar proliferation assays. In some experiments, MTS reagent, Cell Titer 96[®] AQueous One Solution Reagent (Promega Corporation) is added to a final concentration of 333 μ g/mL in place Cell Titer Glo and read at 490/650 nm on a plate reader.

Example C

Cell-Based FGFR Phosphorylation Assays

The inhibitory effect of compounds on FGFR phosphorylation in relevant cell lines (Ba/F3-FGFR3, KMS-11, RT112,

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KatoIII, H-1581 cancer cell lines and HUVEC cell line) can be assessed using immunoassays specific for FGFR phosphorylation. Cells are starved in media with reduced serum (0.5%) and no FGF1 for 4 to 48 h depending upon the cell line then treated with various concentrations of individual inhibitors for 1-4 hours. For some cell lines, such as Ba/F3-FGFR3 and KMS-11, cells are stimulated with Heparin (20 µg/mL) and FGF1 (10 ng/mL) for 10 min. Whole cell protein extracts are prepared by incubation in lysis buffer with protease and phosphatase inhibitors [50 mM HEPES (pH 7.5), 150 mM NaCl, 1.5 mM MgCl₂, 10% Glycerol, 1% Triton X-100, 1 mM sodium orthovanadate, 1 mM sodium fluoride, aprotinin (2 µg/mL), leupeptin (2 µg/mL), pepstatin A (2 µg/mL), and phenylmethylsulfonyl fluoride (1 mM)] at 4° C. Protein extracts are cleared of cellular debris by centrifugation at 14,000×g for 10 minutes and quantified using the BCA (bicinchoninic acid) microplate assay reagent (Thermo Scientific).

Phosphorylation of FGFR receptor in protein extracts was determined using immunoassays including western blotting, enzyme-linked immunoassay (ELISA) or bead-based immunoassays (Luminex). For detection of phosphorylated FGFR2, a commercial ELISA kit DuoSet IC Human Phospho-FGF R2α ELISA assay (R&D Systems, Minneapolis, Minn.) can be used. For the assay KATO111 cells are plated in 0.2% FBS supplemented Iscove's medium (5×10⁴ cells/well/per 100 µL) into 96-well flat-bottom tissue culture treated plates (Corning, Corning, N.Y.), in the presence or absence of a concentration range of test compounds and incubated for 4 hours at 37° C., 5% CO₂. The assay is stopped with addition of 200 µL of cold PBS and centrifugation. The washed cells are lysed in Cell Lysis Buffer (Cell Signaling, #9803) with Protease Inhibitor (Calbiochem, #535140) and PMSF (Sigma, #P7626) for 30 min on wet ice. Cell lysates were frozen at -800° C. before testing an aliquot with the DuoSet IC Human Phospho-FGF R2α ELISA assay kit. GraphPad prism 3 was used to analyze the data. The IC₅₀ values were derived by fitting the data to the equation for a sigmoidal dose-response with a variable slope.

For detection of phosphorylated FGFR3, a bead based immunoassay was developed. An anti-human FGFR3 mouse mAb (R&D Systems, cat#MAB7661) was conjugated to Luminex MAGplex microspheres, bead region 20 and used as the capture antibody. RT-112 cells were seeded into multi-well tissue culture plates and cultured until 70% confluence. Cells were washed with PBS and starved in RPMI+0.5% FBS for 18 hr. The cells were treated with 10 µL of 10× concentrations of serially diluted compounds for 1 hr at 37° C., 5% CO₂ prior to stimulation with 10 ng/mL human FGF1 and 20 µg/mL Heparin for 10 min. Cells were washed with cold PBS and lysed with Cell Extraction Buffer (Invitrogen) and centrifuged. Clarified supernatants were frozen at -800° C. until analysis.

For the assay, cell lysates are diluted 1:10 in Assay Diluent and incubated with capture antibody-bound beads in a 96-well filter plate for 2 hours at room temperature on a plate shaker. Plates are washed three times using a vacuum manifold and incubated with anti-phospho-FGF R1-4 (Y653/Y654) rabbit polyclonal antibody (R&D Systems cat# AF3285) for 1 hour at RT with shaking. Plates are washed three times. The diluted reporter antibody, goat anti-rabbit-RPE conjugated antibody (Invitrogen Cat. # LHB0002) is added and incubated for 30 minutes with shaking. Plates are washed three times. The beads are suspended in wash buffer with shaking at room temperature for 5 minutes and then read on a Luminex 200 instrument set to count 50 events per sample, gate settings 7500-13500. Data is expressed as mean

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fluorescence intensity (MFI). MFI from compound treated samples are divided by MFI values from DMSO controls to determine the percent inhibition, and the IC₅₀ values are calculated using the GraphPad Prism software.

Example D

FGFR Cell-Based Signaling Assays

Activation of FGFR leads to phosphorylation of Erk proteins. Detection of pErk is monitored using the Cellu'Erk HTRF (Homogeneous Time Resolved Fluorescence) Assay (CisBio) according to the manufacturer's protocol. KMS-11 cells are seeded into 96-well plates at 40,000 cells/well in RPMI medium with 0.25% FBS and starved for 2 days. The medium is aspirated and cells are treated with 30 µL of 1× concentrations of serially diluted compounds (diluted with medium lacking serum from 5 mM DMSO dots) to a final volume of 30 µL/well and incubated for 45 min at room temperature. Cells are stimulated by addition of 10 µL of Heparin (100 µg/mL) and FGF1 (50 ng/mL) to each well and incubated for 10 min at room temperature. After lysis, an aliquot of cell extract is transferred into 384-well low volume plates, and 4 µL of detection reagents are added followed by incubation for 3 hr at room temperature. The plates are read on a PheraStar instrument with settings for HTRF. The normalized fluorescence readings are converted to percent inhibition relative to DMSO treated control wells, and the IC₅₀ values are calculated using the GraphPad Prism software. Compounds having an IC₅₀ of 1 µM or less are considered active.

Example E

VEGFR2 Kinase Assay

Enzyme reactions (40 µL) are run in black 384 well polystyrene plates for 1 hour at 25° C. Wells are dotted with 0.8 µL of test compound in dimethyl sulfoxide (DMSO). The assay buffer contains 50 mM Tris, pH 7.5, 0.01% Tween-20, 10 mM MgCl₂, 1 mM EGTA, 5 mM DTT, 0.5 µM Biotin-labeled EQEDEPEGDYFEWLE peptide substrate (SEQ ID NO: 1), 1 mM ATP, and 0.1 nM enzyme (Millipore catalogue number 14-630). Reactions are stopped by addition of 20 µL Stop Buffer (50 mM Tris, pH=7.8, 150 mM NaCl, 0.5 mg/mL BSA, 45 mM EDTA) with 225 nM LANCE Streptavidin Surelight® APC (PerkinElmer catalogue number CR130-100) and 4.5 nM LANCE Eu-W1024 anti phosphotyrosine (PY20) antibody (PerkinElmer catalogue number AD0067). After 20 minutes of incubation at room temperature, the plates are read on a PheraStar FS plate reader (BMG Labtech). IC₅₀ values can be calculated using GraphPad Prism.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

SEQUENCE LISTING

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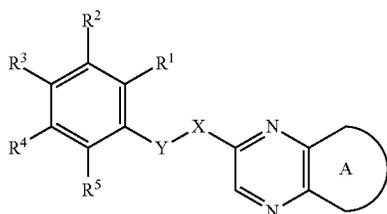
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Glu Gln Glu Asp Glu Pro Glu Gly Asp Tyr Phe Glu Trp Leu Glu

1 5 10 15

What is claimed is:

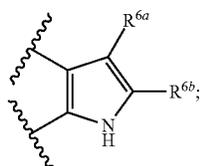
1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X and Y are each independently selected from CH₂, O, and S, wherein no more than one of X and Y is selected from O and S;

ring A is



R¹, R², R³, R⁴, and R⁵ are each independently selected from H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, CN, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from halo, C₁₋₆ haloalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R^e is selected from H, C₁₋₄ alkyl, CN, and C₁₋₄ alkoxy;

R^{6a} and R^{6b} are each independently selected from H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R⁹;

each R⁹ is independently selected from Cy¹, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}; wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, and 4-10

membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}.

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, and R^{d2} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, (5-10 membered heteroaryl)-C₁₋₄ alkyl, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl, (5-10 membered heteroaryl)-C₁₋₄ alkyl, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl are optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}.

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}.

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered

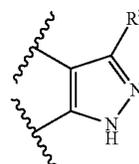
heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, CN, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}C(O)OR^{a3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, and S(O)₂NR^{c3}R^{d3};

each R^{e1} and R^{e2} is independently selected from H, C₁₋₄ alkyl, CN, OR^{a3}, SR^{b3}, S(O)₂R^{b3}, C(O)R^{b3}, S(O)₂NR^{c3}R^{d3}, and C(O)NR^{c3}R^{d3};

each R^{a3}, R^{b3}, R^{c3}, and R^{d3} is independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, wherein said C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, are optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy; and

each R^{e3} is independently selected from H, C₁₋₄ alkyl, and CN.



- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X and Y are both CH₂.
- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is H, halo, C₁₋₆ alkyl, CN, or C(O)NR^{c1}R^{d1}.
- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is H, Br, Cl, CH₃, CH₂CH₃, CN, or C(O)NHCH₃.
- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{6a} is H.
- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{6b} is other than H.
- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{6b} is C₁₋₆ alkyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₅₋₁₀ membered heteroaryl, 4-10 membered heterocycloalkyl, or C(O)NR^{c1}D^{d1}; wherein said C₁₋₆ alkynyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R⁹.
- The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{6b} is propyl, propynyl, phenyl, thienyl, pyrazolyl, pyridyl, pyrimidinyl, benzo[d][1,3]dioxolyl, 1,2,3,6-tetrahydropyridinyl, 1H-indazolyl, piperidinyl, pyrido[2,3-b]pyrazinyl, indolin-2-onyl, C(O)NHCH₃, or C(O)N(CH₃)₂; wherein said propyl, propynyl, phenyl, thienyl, pyrazolyl, pyridyl, pyrimidinyl, benzo[d][1,3]dioxolyl, 1,2,3,6-tetrahydropyridinyl, 1H-indazolyl, piperidinyl,

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pyrido[2,3-b]pyrazinyl, and indolin-2-onyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R⁹.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R⁹ is Cy¹, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, CN, OR^{a1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, NR^{c1}R^{d1}, or NR^{c1}C(O)R^{b1}, wherein said C₁₋₆ alkyl, is optionally substituted with 1, 2, or 3 substituents independently selected from Cy¹, halo, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1}.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least two of R¹, R², R³, R⁴, and R⁵ are other than H.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least three of R¹, R², R³, R⁴, and R⁵ are other than H.

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least four of R¹, R², R³, R⁴, and R⁵ are other than H.

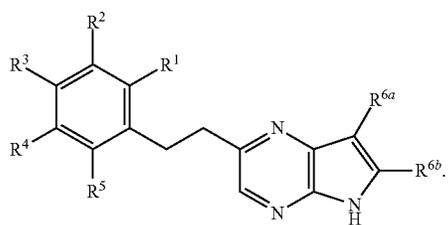
13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, and R⁵ are each independently selected from H, halo, and OR^a.

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, and R⁵ are each independently selected from H, F, and OCH₃.

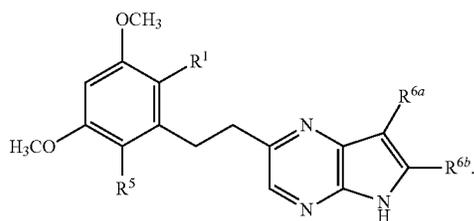
15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is H, R² is OCH₃, R³ is H, R⁴ is OCH₃, and R⁵ is H.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R¹ is F, R² is OCH₃, R³ is H, R⁴ is OCH₃, and R⁵ is F.

17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having Formula IIa:



18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having Formula IIb:



19. The compound of claim 1 selected from:

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

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2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-ethylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-(3,5-dimethoxyphenethyl)-6-phenyl-5H-pyrrolo[2,3-b]pyrazine;

6-(2,6-difluorophenyl)-2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(4-methoxyphenyl)-5H-pyrrolo[2,3-b]pyrazine;

N-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}phenyl)acetamide;

4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-dimethylbenzamide;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(trifluoromethyl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(2-methylphenyl)-5H-pyrrolo[2,3-b]pyrazine;

2-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}benzotrile;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(piperidin-1-ylmethyl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(methoxymethyl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}phenyl)methanol;

(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}phenyl)acetonitrile;

4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}benzoic acid;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[6-(4-methylpiperazin-1-yl)pyridin-3-yl]-5H-pyrrolo[2,3-b]pyrazine;

5-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N-methylpyridine-2-carboxamide;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[5-(morpholin-4-ylcarbonyl)pyridin-3-yl]-5H-pyrrolo[2,3-b]pyrazine;

4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}thiophene-2-carboxylic acid;

5-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-dimethylpyrimidin-2-amine;

6-(1,3-benzodioxol-5-yl)-2-[2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazine];

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(1-methylpiperidin-4-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methylpiperidin-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-5H-pyrrolo[2,3-b]pyrazine-6-carb oxamide;

2-[2-(3,5-dimethoxyphenyl)ethyl]-N,N-dimethyl-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide;

3-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-diethylprop-2-yn-1-amine;

3-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-N,N-diethylpropan-1-amine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-(1-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(2-morpholin-4-ylethyl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine;

1-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-2-methylpropan-2-ol;

2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-N,N-dimethylethanimine;

3-cyclopentyl-3-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)propanenitrile;

3-(4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)butanenitrile;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine;

2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)ethanol;

(2S)-1-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)propan-2-ol;

1-[2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)ethyl]piperidin-4-ol;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-(2-piperidin-1-ylethyl)-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[1-[2-(4-methylpiperazin-1-yl)ethyl]-1H-pyrazol-4-yl]-5H-pyrrolo[2,3-b]pyrazine;

2-(4-{2-[2-(3,5-dimethoxyphenyl)ethyl]-5H-pyrrolo[2,3-b]pyrazin-6-yl}-1H-pyrazol-1-yl)-N,N-dimethylacetamide;

2-(4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)-1-(4-methylpiperazin-1-yl)ethanone;

2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine-7-carbonitrile;

7-bromo-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

7-chloro-2-[2-(3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(2-chloro-3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(2,6-dichloro-3,5-dimethoxyphenyl)ethyl]-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-N-methyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine-7-carboxamide;

2-[2-(3,5-dimethoxyphenyl)ethyl]-7-methyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(3,5-dimethoxyphenyl)ethyl]-7-ethyl-6-[4-(4-methylpiperazin-1-yl)phenyl]-5H-pyrrolo[2,3-b]pyrazine;

2-Chloro-4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N-isopropylbenzamide;

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-fluoro-N,N-dimethylbenzamide;

2-(3,5-Dimethoxyphenethyl)-6-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-Chloro-4-(2-(3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N,N-dimethylbenzamide;

4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-fluoro-N-methylbenzamide;

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyrimidin-2-amine;

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N,N-dimethylpicolinamide;

4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)picolinonitrile;

2-(3,5-Dimethoxyphenethyl)-6-(6-methoxypyridin-3-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(3,5-Dimethoxyphenethyl)-6-(1-methyl-1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(3,5-Dimethoxyphenethyl)-6-(1-methyl-1H-indazol-6-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(3,5-Dimethoxyphenethyl)-6-(2-(piperazin-1-yl)pyridin-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-fluorobenzonitrile;

7-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyrido[2,3-b]pyrazine;

N-(5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-2-yl)acetamide;

1-(5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-2-yl)pyrrolidin-2-one;

4-(5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-3-yl)morpholine;

2-(3,5-Dimethoxyphenethyl)-6-(1H-indazol-5-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(4-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)piperazin-1-yl)ethanol;

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-2-(4-methylpiperazin-1-yl)benzoxonitrile;

4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N-methylpicolinamide;

4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-N,N-dimethylpicolinamide;

(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)pyridin-2-yl)(3-hydroxyazetidin-1-yl)methanone;

1-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)-4-methylpiperazin-2-one;

1-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)piperidin-4-ol;

2-(3,5-Dimethoxyphenethyl)-6-(3-(piperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine;

2-(3,5-Dimethoxyphenethyl)-6-(3-(4-methylpiperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine;

5-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)indolin-2-one;

4-(4-(2-(3,5-Dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)phenyl)-1-methylpiperazin-2-one;

2-(2-Fluoro-3,5-dimethoxyphenethyl)-6-(4-(4-methylpiperazin-1-yl)phenyl)-5H-pyrrolo[2,3-b]pyrazine;

2-[2-(2,6-difluoro-3,5-dimethoxyphenyl)ethyl]-6-(5-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(2,6-difluoro-3,5-dimethoxyphenethyl)-6-(1-methyl-1H-pyrazol-4-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)benzoxonitrile;

2-(2,6-difluoro-3,5-dimethoxyphenethyl)-6-(2-methoxypyridin-3-yl)-5H-pyrrolo[2,3-b]pyrazine;

2-(4-(2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)-N,N-dimethylethanimine;

1-(4-(2-(2,6-difluoro-3,5-dimethoxyphenethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol; and

2-(2,6-difluoro-3,5-dimethoxyphenethyl)-N-methyl-5H-pyrrolo[2,3-b]pyrazine-6-carboxamide, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

21. A method of modulating fibroblast growth factor receptor activity in a patient comprising administering to said patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,388,185 B2
APPLICATION NO. : 13/963569
DATED : July 12, 2016
INVENTOR(S) : Lu et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page

Item [56], Col. 2, Line 12, delete “syndryome” and insert -- syndrome --.

In the claims

Col. 96, Line 56, Claim 7, delete “C₁₋₆ alkynyl,” and insert -- C₁₋₆ alkyl, C₂₋₆ alkynyl, --.

Col. 99, Lines 7-8, Claim 19, delete “5H-pyrrol o[2,3-b]” and insert -- 5H-pyrrolo[2,3-b] --.

Col. 100, Line 4, Claim 19, delete “5H-pyrrol o[2,3-b]” and insert -- 5H-pyrrolo[2,3-b] --.

Col. 100, Line 18, Claim 19, delete “(3, 5-Dimethoxyphenethyl)” and insert -- (3,5-Dimethoxyphenethyl) --.

Col. 100, Line 29, Claim 19, delete “(3, 5-Dimethoxyphenethyl)” and insert -- (3,5-Dimethoxyphenethyl) --.

Col. 100, Line 31, Claim 19, delete “(3, 5-Dimethoxyphenethyl)” and insert -- (3,5-Dimethoxyphenethyl) --.

Signed and Sealed this
Twenty-ninth Day of November, 2016



Michelle K. Lee
Director of the United States Patent and Trademark Office

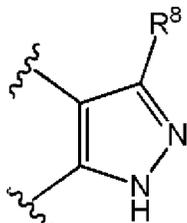
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Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims



Column 96, Lines 30-39, Claim 1, delete “ ,”.

Signed and Sealed this
Third Day of January, 2017

Michelle K. Lee
Director of the United States Patent and Trademark Office